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GUY'S HOSPITAL REPORTS

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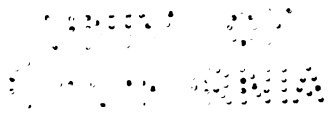

Golding Bird

GOLDING BIRD

ASSISTANT PHYSICIAN TO GUY'S HOSPITAL, 1843 TO 1854.

By SIR WILLIAM HALE-WHITE, K.B.E., M.D., Consulting Physician to Guy's Hospital.

GUY'S has often been unfortunate in that some of its physicians have died early. One of these was Golding Bird, who was born at Downham in Norfolk on December 9, 1814. His father, also named Golding Bird, who held office in the Inland Revenue Department, had spent much of his life in Ireland and had married an Irish lady. He had two daughters and three sons, all now dead, except one daughter who is almost a centenarian. One son was Dr. F. Bird, to be mentioned presently. Another was for many years vicar of St. Bartholomew's Church, Gray's Inn Road; he was the father of the present Bishop of Mauritius and of a son who became a student at Guy's, but died in his youth.

The remaining son, the frail future physician, Golding, was, while still young, placed in the family of a clergyman at Wallingford in Berkshire. He quickly showed his aptitude for acquiring knowledge, so that when, at the age of twelve, he was sent, with his brother, F. Bird, to a private school in London, he was well versed in classical and general learning. Here he studied botany and chemistry; such was his enthusiasm that, with his brother as his assistant, he conducted classes in these subjects among his school-fellows at an early hour before regular school began. The cheapest chemical reagents, some broken glasses, an old lamp and a blow-pipe formed his laboratory; a few poppy-heads and a few garden flowers his herbarium. These proceedings were stopped by the schoolmaster, and this led to so much ill feeling between him and the two brothers that they were removed from the school. Both became doctors, and in after life, by a strange chance, one was called to the death-bed of the master, the other to that of his wife, an opportunity being thus given of healing the rancour which arose between the master and the brothers on account of what they considered unjust treatment. Golding's brother, Dr. F. Bird, was a distinguished member of the profession, holding the post of Obstetric Physician to the Westminster Hospital. Many articles by him, generally of gynæcological interest, are to be found in contemporary medical literature.

On December 23, 1829, Golding Bird was apprenticed for four years to Mr. William Pretty, an apothecary of Mabledon Place, London. We have no account of his life here, except that as so much of the day was occupied with routine duties, he sat up far into the night to study.

In 1832 he became a pupil at Guy's Hospital, but his articles with Mr. Pretty were not cancelled until October 12, 1833, so that for a year he appears to have continued to work with Pretty while studying at Guy's. Like some other students, he took his courses one by one. The books of the Guy's Medical School show that the first was chemistry, taken out September 1832; the others were taken out in the following order between February 1833 and January 1834—Materia Medica, Anatomy, Dissections, Botany, Surgeon's Pupil, Practice of Medicine, Medical Pupil, and Physician's Practice. His talents and unusual industry attracted the attention of both Addison and Astley Cooper. The first wrote of him, "I have ever regarded with wonder and admiration his extraordinary industry, his powers of memory and vast acquirements, not only in the various departments of his profession, but in every science or branch of knowledge connected with it." Golding Bird, on his part, had a great reverence for Addison. He dedicated his work on *Urinary Deposits* to him, and says, "It is now thirteen years since I found myself within the walls of Guy's Hospital, a stranger and unknown. In a short time my admiration and respect were excited for your profound knowledge and experience as a physician, and for your zeal as a teacher. But I soon experienced another feeling—that of gratitude for numerous acts of the most disinterested friendship, and for which I must ever remain your debtor." Astley Cooper showed his appreciation of Golding Bird's ability by asking him to write on the chemistry of milk in his work on *Diseases of the Breast*. Whilst at Guy's, Golding Bird's facility for teaching demonstrated itself in the classes he held for his fellow-students. He obtained numerous school prizes, distinguished himself at the Physical Society, where he was awarded the Honorary Diploma of the Society on May 7, 1836, Bright being in the chair, and he gained the botanical prize given by the Apothecaries' Society. On January 21, 1836, when barely twenty-one, he presented himself for examination for the diploma of this body. His reputation had preceded him, and, because of it, the examiners gracefully declined to examine, but presented him with his licence and also wrote to the authorities of Guy's to express their high appreciation of his merits.

Golding Bird was a man of middle height and of a singularly

delicate conformation. As Wilks tells us, no man could have worked harder under such trying physical disabilities. Payne, in his article in the *Dictionary of National Biography*, sums up the matter well by saying, "There can be little doubt that Bird did too much. His foible was perhaps ambition, which led him to overstrain his powers in the twofold effort to obtain a large practice and also to make a name in science." This ambition, overrunning the frail body, was seen even in his student days, for, to the hard work of an exceptionally diligent student and popular coach, he added that of writing original papers. He began early, for on September 17, 1832, almost at the exact date of his entry as a student at Guy's, and when not yet eighteen years old, he wrote a short article on the analysis of coffee and rye.[1] Soon after there appeared an article [2] showing that the method of extracting the alkaloid from conium given in the text-books was incorrect, and telling how it should be done properly. Several of the papers published during his studentship were in collaboration with his future brother-in-law, R. Hargrave Brett, who became a chemist of note and lectured at the Royal Institution. They are as follows: *On the Chemical Constitution of the Urine in Various Diseases*,[3] an admirable short account; *The Chemical Analysis of the Serum of the Blood;* [4] *The Chemical Analysis of Serum and Urine in Disease*; [5] *Analysis of the Fluid of a Hydrocele*; [6] *On Urea, Nitro-Stearic Acid, etc.*,[7] a controversy with G. Owen Rees of Guy's Hospital; *Animal Chemistry*,[8] in which the controversy is continued. In Owen Rees' letters Brett and Golding Bird are rebuked for want of respect to authority. In *Pink Deposits of the Urine* [9] Brett and Golding Bird claimed to show that the pink colour of the urine was not due to purpurates, which, they alleged, was the opinion of Prout. He replied on p. 641 that the young authors had misunderstood him. He gave them a piece of advice coming from "an old chemist," namely, to have a knowledge of the points under discussion before embarking on it. They answered on p. 751, sticking to their guns and claiming that they were supported by Berzelius. *On the Colouring Matter of the Blood;* [10] a new colouring matter of the blood had been described and called sub-rubine; Brett and Golding Bird's long paper goes to show that on chemical grounds there is no such substance, sub-rubine being really one of the known blood pigments. *On the Action of Acids on the Blood;* [11] in this long paper the authors point out that their results are different from those of Berzelius, but they cannot explain the discrepancy. During this period Golding Bird also wrote papers by himself. There is a very severe letter [12] combating a communication

from Dr. Clanny in which he claimed that it helped diagnosis to make a chemical examination of the blood in cases of cholera. A year later there appeared *Modification produced by Castor Oil in passing through the Bowels;*[13] Bright, working at the subject of fatty stools, asked Golding Bird to examine the stools of a woman who had retained an enema of castor oil for twenty-four hours, and then passed a motion containing obvious castor oil together with solid tallow-like masses, which Golding Bird showed to be castor oil that had undergone saponification in the bowel. He followed with *Observations on the Fatty Matter of the Blood,*[14] a long article in which he concludes that cholesterine is not a constituent of normal blood, and *On Certain New Combinations of Albumen.*[15, 16]

I have briefly given all these particulars of his activities during his studentship to prove that young Golding Bird was precocious, extraordinarily able, exceedingly industrious, ambitious, and possessed of a leaning to and an unusual knowledge of chemistry. After his name in the last paper he puts the letters F.L.S. and F.G.S., so he had obtained these distinctions by the age of twenty-one.

At the same age he entered on the period during which he was a teacher in the Medical School, but not on the staff of Guy's, for he was appointed to lecture on " Natural Philosophy, Electricity, Galvanism and other branches of Experimental Philosophy applicable to Medicine." The lectures were given on Mondays at eight in the evening, the fee for each course being one guinea. By 1840 this cumbersome title was altered to " Medical Physics," and in 1844 Gull took over the lectures on this subject. Golding Bird in 1839 published a famous text-book, *Elements of Natural Philosophy.* It completely displaced a book by Mrs. Mary Somerville, which had previously been the favourite. The third edition was published in 1848 simultaneously in England and America. The fourth edition, appearing in 1854, was edited by Charles Brooke, as was the fifth, published in 1860, and the sixth and last, which is dated 1867. Each edition was favourably reviewed in all the medical journals, and the opinion was expressed that the book ought to be in every boys' and every girls' school in the kingdom.

All this teaching and writing on the subject led to his taking especial interest in the application of electricity to medicine, and in 1841 he published *A Report on the Value of Electricity as a Remedial Agent in the Treatment of Diseases.*[17] This paper is of considerable importance, for it did much to rescue medical electricity from quackery and to instruct doctors as to its use. Up to this time, many, when they could do nothing more for a

patient, issued the mysterious order, " Let him be electrified." In October 1836 the Treasurer to the Hospital, Mr. Harrison, set aside and thoroughly equipped a room for electrical treatment. Golding Bird was placed in charge, a clinical clerk kept notes of every case and of its progress. Golding Bird's *Report* gives the result of over four years' working of the department: nearly a hundred cases are recorded, each group is criticised, and we are told when to expect benefit and when the treatment is useless. In 1846 there appeared in the *Lancet* [18] from his pen an article *On the Employment of Electro-magnetic Currents in the Treatment of Paralysis.* This is entirely clinical; in it he strongly reprobates the prevalent quackery on the subject of electricity. A little later in the same journal is an article [19] by him on *The Electric Moxa.* In 1847 the author followed up the same subject by giving before the Royal College of Physicians a course of five lectures on " Electricity and Galvanism in their Physiological and Therapeutic Relations." These were fully reported in *The Medical Times and Gazette* for 1847 and were republished in book form.

In 1851 [20] he wrote an account of his experience with one example of Pulvermacher's Hydro-Electric Chain. This he considered decidedly useful in clinical work, but he was vexed because there was so much quackery in the way it was brought before the profession. He gave a private letter of introduction to someone interested in medical electricity; in it there occurred a sentence which, taken from its context in a private letter, was used as an advertisement of Pulvermacher's Belts. This led to a complaint of his conduct in *The British Medical Journal.*[21] He was very angry, and wrote a letter which showed how his private letter had been treated and that he had never advertised these chains. The matter worried him much, and he received many hundreds of letters on the subject.

He published many purely scientific papers on the subject of electricity. They are: *Observations on the Crystallisation of Metals by Voltaic Action independent of the Proximity of Metallic Electrodes,*[22] *Observations on the Electro-Chemical Influence of long-continued Electric Currents of Low Tension,*[23] *Notice respecting the Artificial Formation of Basic Chloride of Copper by Voltaic Influence,*[24] *Notice respecting the Deposition of Metallic Copper from its Solutions by Slow Voltaic Action at a point equidistant from the metallic surfaces,*[25] *On certain Properties acquired by the Platina Electrodes of a Voltaic Battery,*[26] *Observations on Induced Electrical Currents with a description of a Metallic Contact Breaker,*[27] and lastly an article connected with electricity which appeared in Calcutta.[28]

We have seen that as a school-boy he was fascinated by botany, and that he early became a Fellow of the Linnæan Society. When he arrived at Guy's he attended lectures on this subject by Mr. C. Johnson. It was then the custom for the lecturer to take the students on botanical excursions. These were usually in the neighbourhood of the Albany Road and the Surrey Canal in Walworth, this district being then open fields. Later on Golding Bird became a co-lecturer with Johnson. The Hospital prospectus tells us that these two lectured on the subject in 1837 daily at eleven, the botanical portion being given by Johnson and the therapeutical by Golding Bird. In some of the botanical excursions Golding Bird was accompanied by Miss Brett, his betrothed, and she became an enthusiastic and admirable botanist. His affection for botany never left him; he made a perfect herbarium of dried British plants, and when in the country and at the seaside he always pursued this study. In Balfour's biographical sketch of Golding Bird [29] there is a good description of how, in 1853, he hunted with great ardour for specimens on the seashore at Tenby, and of his joy at becoming the possessor of what was the best microscope then made—a Powell and Leland with an eighth-inch object glass. He sometimes amused himself by dipping a piece of paper in a solution of silver nitrate, placing a fern on this, and then exposing the paper to the sun, by which means he obtained a pattern of the fern on the paper. He published an article on this subject entitled, *Observations on the application of Heliographic or Photogenic Drawing for Botanical Purposes.*[30]

A few papers from him show his interest in botany—*Remarks on a particular Form of Irritability observed in the Stems of many Plants, especially Exogens, evinced on dividing them in the direction of their axis,*[31] and *Observations on the Existence of Saline Combinations in an Organic State in Vegetable Structures.*[32] We also find him publishing *On the Siliceous Armour of Equisetum hymenale, with an account of a hitherto undescribed Stomatic Apparatus,*[33] and *Remarks on the preparation of Polypidoms of Zoophytes for microscopical examination, with a notice of the phenomena they exhibit with polarised light.*[34]

He continued to be an active member of the Physical Society. During the Session 1836–37 he was awarded the Society's Prize for an *Essay on Pathological Chemistry as applicable to the Diagnosis of Disease*, and in February 1839 he read a paper entitled *Observations on the Pathology of Death from Charcoal Vapour.* It provoked a good discussion and was published.[35] It is a long, comprehensive and interesting paper, in which the author contends that persons killed by the vapour do not die from

interference with respiration owing to the carbonic acid, but that this acts as a specific poison to the nervous system. He tells how seventy persons were poisoned in Downham Church in Norfolk owing to the use of Joyce's patent stove, an apparatus in which charcoal was burnt, but the products of combustion escaped into the apartment it heated.

We find him taking part in many of the Society's discussions, such as those on humoral pathology, medical statistics, the functions of the pericardium, and the medicinal properties of plants. In 1836 he describes himself as " Senior Fellow of the Physical Society." He was President for the Session 1849–50.

In the period following 1836 he was a frequent contributor to the *Guy's Hospital Reports*. Addison in his classical paper on *Fatty Degeneration of the Liver* [36] gives the analysis of the liver, bile and urine " furnished by my friend Mr. Golding Bird." In 1838 he himself published there his *Researches into the Chemical Nature of Mucous and Purulent Secretions*.[37] This is very learned, shows much hard work, and contains many references to his prize essay read before the Physical Society and to a paper he published in the *Philosophical Transactions*.[38] In 1840 [39] there appeared from his pen *Observations on the existence of certain elements of the Milk in the Urine during Utero-Gestation*. He shows that the so-called kiestin, said to be present in the urine of pregnant women, consists of organic matter associated with organic phosphates. This he believes to be a very valuable corroborative indication of pregnancy.

Golding Bird is best remembered for his publications concerning urinary calculi and deposits. The first volume of the Guy's *Reports* contains a paper by him entitled *Remarks on Cystine or Cystic Oxide*.[40] He gives the analysis of a cystine calculus Mr. Key had removed; he announces that he detected cystine in the urine of the patient, and he thinks that perhaps it enters into the composition of calculi more commonly than is generally supposed. Six years later he published a very long, laborious and thorough article, *Observations on Urinary Concretions and Deposits with an account of the Calculi in the Museum of Guy's Hospital*.[41] Twenty-five years previously Marcet had described the calculi in the Guy's Museum. Golding Bird records the analyses of those added since; he had the great advantage over Marcet that the microscope had come into use. He gives beautifully coloured plates. In the same year there appeared a short *Note on the Microscopic Globules found in Urine*.[42]

Following all this work, he, in the early part of 1843, delivered at Guy's Hospital a course of lectures *On the Diagnosis and*

Pathology of Urinary Sediments. These were reported in the *London Medical Gazette.*[43] Soon they, together with his papers in the Guy's *Reports*, were translated into German. The perusal of this translation induced him to write his well-known book, *Urinary Deposits, their Diagnosis, Pathology and Therapeutical Indications*, dated from Myddleton Square, October 20, 1844. It is an excellent text-book with illustrative cases. It was very well reviewed and went through four editions edited by the author, and a fifth, published in 1857, edited by Dr. Lloyd Birkett, who had been Curator of the Museum at Guy's and Secretary to the Clinical Society. This edition is dedicated to Dr. G. H. Barlow; the first had been dedicated to Addison. In each edition the book grew, the final fifth edition being more than a third as long again as the first.

In 1840 the *London Medical Gazette* [44] reprinted the article on *Milk* he had written for Astley Cooper, and in the same volume is a paper by Golding Bird *On the occurrence of Cerebral Disorders in connection with Diseased Kidneys in Children.*[45] In this he suggests that coma in children is sometimes due to uræmia, they having unsuspected nephritis following scarlet fever, which was very prevalent at this time.

He wrote an article entitled *On the advantages of a Stethoscope with a flexible tube.*[46] This contains a discussion on the physical properties of the stethoscope. He says Clendinning and Stroud had used a common snake-hearing trumpet, but he thinks that his form of flexible stethoscope is better. It consisted of an ebony chest-piece, a flexible tube, sixteen to twenty inches long and a quarter of an inch in diameter, made of spiral iron wire covered with rubber and silk and having an ear-piece of ebony. John Burne [47] seemed to consider Golding Bird might have said that he, Burne, had used a flexible stethoscope for some time at the Westminster Hospital. This was construed by Golding Bird as implying that he claimed to be the first to use a flexible stethoscope, so he wrote an angry, and perhaps over-severe, letter,[48] denying priority, and saying, which was true, that he had never claimed this, but it is only fair to add that Burne had not accused him of claiming it.

A little later there appeared a very long communication, *A Contribution to the Chemical Pathology of some forms of Morbid Digestion.* It really consisted of six articles.[49] This is one of his best papers. He shows that black vomit is so coloured because it contains blood, and he urges the importance of examining the contents of the stomach for blood, especially if the patient is anæmic. He is sceptical as to drawing conclusions from chemical examination of the contents of the stomach

when organic disease is absent; he points out that the reaction varies in the same person at different times; thus he foreshadows one of the things we have learned from fractional test-meals, and he was the first to show that hydrochloric acid is absent from the gastric secretion in some cases of malignant disease of the stomach. His words are: "It would certainly appear that *pari passu* with the extension of the disease (malignant) the hydrochloric acid disappears and the organic acids increase." This is a thoroughly scientific series of papers. The saliva and gastric secretion in both health and disease are described, and there are many illustrative cases.

These papers were followed by another long communication, *Researches into the Nature of Certain Frequent Forms of Disease characterised by the presence of Oxalate of Lime in the Urine.*[50] The author concludes that oxalate of lime is not formed from saccharine matter, but is a result of the re-arrangement of the elements of urea, which, under the influence of disease, has been formed in excess in the system. He considers that, as rhubarb contains oxalates, the eating of it gives rise to a liability to oxalate of lime calculus, and, as he found oxalate of lime in the preputial secretion in small boys, he suggested that the balanitis from which they suffer is due to oxalate of lime.

From the medical journals we learn that at this period he was an active member of the Westminster Medical Society, before which he read papers on *Poisoning by Carbonic Oxide,*[51] *Alcoholic Poisoning, Elaterine,* and *Anæmia and Hyperæmia,*[52] and at which he showed many clinical cases. Later on he was President of the Society.

His interest in chemistry is shown by several other papers published during the period under consideration. We find these: *On Certain New Combinations of Albumen,*[53] *Experimental Researches on the Nature and Properties of Albumen,*[54] *Observations on some of the Products obtained by the Action of Nitric Acid on Alcohol,*[55] *On Indirect Chemical Analysis,*[56] *On the Action of Nitric Acid on Alcohol,*[57] *Account of the Researches of Mons. R. Piria on the Combination of Salicyle,*[58] *Remarks on Dr. Stark's Statements of the Animal Matter of the Urine in Pregnancy,*[59] *On Certain Fallacies in Enderlius' Researches on the Saline Constituents of Animal Fluids,*[60] and with Brett, *On the Existence of Titanic Acid in Hessian Crucibles.*[61]

All his lecturing and teaching at Guy's, his hard work at original investigations, and the numerous papers he wrote did not prevent his pursuit of clinical medicine. He was physician to the Finsbury Dispensary from 1838 to 1843; for part of this time he also held the post of physician to the Islington Dispen-

sary, and we find him, in 1841, lecturing on the Theory and Practice of Medicine at the Aldersgate Medical School. In 1839 he was one of the Secretaries of the Chemical Section of the British Association at the meeting held in Birmingham.

Directly after obtaining the L.S.A., in 1836, he started in general practice at 44 Seymour Street, Euston Square, but, as might be expected, being only twenty-one and young-looking at that, no patients came. He therefore abandoned general practice and determined to become a physician. He was encouraged in this by the high opinion of him which had been formed by the authorities at Guy's Hospital. In his diary we find this note : " In 1838, at the suggestion of the Hospital authorities, I went to Scotland and passed the examination for the degree of M.D. at St. Andrews, and shortly after the publication of my manual on Natural Philosophy was presented with the honorary degree of M.A." He found time in 1840 to pass the examination for the Licentiateship of the Royal College of Physicians. Four years later, that is in the shortest time possible, he was elected a Fellow. At the end of one of his publications he calls himself M.R.C.S., so he must have taken this qualification also.

We have learnt that, owing to the suggestion of the authorities of Guy's, he took the degree of M.D.; we have quoted Addison's opinion of him, and have indicated his extraordinary literary output and his overwhelming industry, and further we have seen that at an early age he was appointed a lecturer in the Medical School in two subjects. It is, therefore, not a matter of surprise that, when Bright retired in 1843, Golding Bird was appointed Assistant Physician to Guy's Hospital; thus, to his great joy, he realised one of his several ambitions. He was devoted to Guy's and proud of it. His eldest child was named Guy. Three years later, namely, in January 1846, he was elected an F.R.S. He was a corresponding member of the Institut d'Afrique, a corresponding member of the Philosophical Institute of Basle, a member of the Philosophical Society of St. Andrews, a member of the Medical Society of Hamburg, and Lecturer on Materia Medica at the Royal College of Physicians.

Shortly after becoming Assistant Physician to Guy's Hospital, having given up lecturing on Natural Philosophy, he joined Addison in lecturing on Materia Medica on Tuesdays, Thursdays and Saturdays at half-past three. During the Session 1846–7 he retired from lecturing on botany and became sole lecturer on Materia Medica, but by 1850 Owen Rees had become his co-lecturer on this subject. For a short time he helped Addison in the lectures on Medicine, taking the subject

of urinary diseases. In 1849 a vacancy occurred for the Professorship on Medicine at University College. Golding Bird's ambitious nature made him desire this, for, with Addison in front of him, the prospect of his having the full lectureship at Guy's was remote. He went so far as to collect testimonials from Bright, Addison, Bransby Cooper, Hilton and Owen Rees. All these are before me, and they show the exceedingly high position Golding Bird held in the estimation of his colleagues and their regret that he should think of leaving Guy's. Probably this last made him withdraw his candidature, for we hear nothing more of the matter.

This is the most suitable place in which to describe a matter of considerable interest in the history of Guy's Hospital, namely, the formation of a children's department.

There is in the *Guy's Hospital Reports* for 1845 [62] an article by Golding Bird entitled *Report on Cases of Diseases of Children treated at Guy's Hospital.* He tells us that previously Dr. Barlow, with the consent and help of the Treasurer, Mr. Harrison, had arranged for a children's out-patient department. Golding Bird succeeded Barlow as physician in charge of this department. If necessary, children were admitted into beds specially appropriated to children. From the paper it is apparent that nearly all these beds were under the charge of Golding Bird. The size of the department is shown by the fact that from October 1843 to January 1845, 830 children were treated as out-patients and 75 were admitted as in-patients. The author gives an account of the more interesting cases. He extols the value of Pulvis Rhei Salinus, the anti-hectic powder of Fordyce, from whom he gives this delightful quotation: "Had I been more ambitious of dying a rich man, than of living a useful member of society, the power of our anti-hectic powder in curing, as if by a miracle, the hectic fever and the swelled bellies of children of this town, would have remained a secret while I lived." In the *London Medical Gazette* [63] seven years later there appeared a leading article suggesting a children's hospital for London. Golding Bird at once wrote a letter to this periodical, to emphasise the importance of the study of children's diseases, and to regret the scant attention paid to the subject in the current text-books, but he reminds the profession that, owing to the initiative of Dr. Barlow and the powerful help of Mr. Harrison, there has been at Guy's for several years a special children's department. He tells us that the "Take in" day is Friday, that there are clinical clerks attached to the department, and that proper notes of the cases are recorded. Often more than sixty cases are seen on a single out-patient day. There are thirteen beds in a special

ward for children's diseases and clinical lectures are given on this subject. The total number of children attending as out-patients in one year was 700, and 150 were admitted as in-patients. Thus it appears that, in Golding Bird's time, this was a flourishing department of the Hospital, which had grown considerably under his guidance.

He was now Assistant Physician to the Hospital, he was in charge of two special departments—namely, those of electricity and children's diseases—he held two lectureships, had to see new editions of his text-book on Natural Philosophy through the press, was writing his book on *Urinary Deposits*, and was conducting a very large private practice, so with all this work his previous flow of papers, although still considerable, became a trifle lessened.

In the *London Medical Gazette* the following appeared: "*A Case in which Enlarged Bronchial Glands caused Death by Pressure on the Bronchus.*[64] *On some criticisms on a late review in the British and Foreign Medical Review;* this is a long argumentative article in which Golding Bird seeks to destroy certain opinions expressed by Ansell.[65] *An account of Professor Mulder's researches on the existence of Oxides of Protein in the Blood;* [66] this is a long critical review. *Remarks on the respective value of the different tests for the Detection of a Diabetic State of the Urine;* [67] in this article the tests are critically examined, and Golding Bird concludes that their order of usefulness is Trommer's test, growth of torula, development of fermentation and Runge's sulphuric test. *Remarks on Fatty Urine;* [68] in this he records a case of milky-looking urine in which no fat globules could be seen under the microscope. *Remarks on Professor Liebig's Views of the Composition of the Urine;* [69] this is a long critical review. *An Account of Professor Mulder's Researches on the Chemical Physiology of the Red Colouring Matter of the Blood.*[70] *On the Crystalline form of the Carbonate and on Oxalate of Lime in the Urine of Herbivora;* [71] he pleads for further investigation and announces that he had discovered both the above in the urine of the horse. *On the mode of ascertaining the Proportion of Solids existing in the Urine.*[72] *On the Nature of the Green Alvine Evacuations of Children;* [73] the author regards the green colour as due to altered blood. *On the nature and character of Dumb-bell Crystals described as Oxalate of Lime;* [74] an American observer had said that these were uric acid, but Golding Bird shows that he is wrong. An *Analysis of the Fatty Matter found in the Ovaries and Uterus.*[75] *Prolapse of the Anterior Wall of the Vagina an occasional cause of Fœtid Phosphatic Mucous Urine.*[76] *On the Rarity of True Inflammatory Croup, On Anasarca after Scarlet Fever,* and

On Anomalous Symptoms following Scarlet Fever, all three in the *Dublin Journal*.[77] After he came on the staff of the Hospital he read many papers before the Medical Society. *A Case of Pericarditis;*[78] and a paper *On the therapeutic influence of warm moist Air in the Treatment of Inflammation of the Air Passages*.[78,79] He participated in a debate at the same Society on "Diet,"[80] and in 1847 he delivered the Annual Oration before the Medical Society,[81] in which he discussed the subjects of the social relationship between the different branches of the profession, the great advances in medical education and the prevalence of quackery. The next year, before the same Society, he read a paper *On Poisoning by Aconite*,[82] and the year after one on *Œdema of the Uvula*[83] and one on *A New Form of Vapour Bath*.[84]

In 1846 he showed before the Royal Medico-Chirurgical Society *A Case of Excessive Secretion of Ammonium Magnesium Phosphate by the Kidneys with long-continued Vomiting*.[85] The case was brought forward to show the importance of vomiting as a symptom of calculus of the kidney. The next year he read before the same Society *An Account of a Case of Internal Strangulation of the Intestine relieved by Operation*.[86] This is an important paper. Golding Bird had been called into the country to see a man suffering from obstruction of the bowel; he had been ill some days, had had many aperients, and had even been given liquid mercury. Golding Bird recognised that there was an internal strangulation and that therefore only surgery gave any hope. Accordingly he took Hilton down to see the case; he agreed with the diagnosis, opened the abdomen and relieved the strangulation. The patient died, as might have been expected, considering that many days had intervened between the onset of symptoms and the operation, but the paper is of historical value; it shows Golding Bird as a bold physician, skilful in diagnosis, and Hilton as a pioneer surgeon in abdominal surgery. A very good discussion followed the reading of the communication, which attracted much attention.

Before the introduction of salicylates rheumatic fever was such a painful tedious disease that Sir Thomas Watson declared that the best treatment for it was six weeks. Hence almost every physician tried something to shorten and alleviate it. A report of cases treated with acetate of potash under Golding Bird at Guy's Hospital was reported in the *Lancet*.[87]

He gave a course of six lectures before the Royal College of Physicians, taking for his title, "On the Influence of Researches in Organic Chemistry on Therapeutics." These were fully

reported at the time of delivery.[88] He gave the Introductory Lecture at Guy's Hospital at the commencement of the Session 1846–47. His son, Mr. C. H. Golding Bird, has a copy of it, and he tells me that it is very long and must have taken two hours to deliver.

In February 1854, the year of his death, although very ill and suffering greatly, he attended a meeting of the Metropolitan Counties Branch of the British Medical Association, which had been convened to protest against the dismissal of Mr. Gay from his post of surgeon to the Royal Free Hospital. The profession considered that he had been wrongfully dismissed. Dr. Risdon Bennett proposed and Golding Bird, in an excellent speech, seconded a motion of protest against the action of the hospital authorities.[89]

During the later part of his life he had two activities outside science and medicine. One was freemasonry; he became a freemason in 1841 and a Royal Arch Mason in 1847, but in 1853 he ceased to be connected with the Craft.

The other flowed from his thoughts on religious matters. We learn from "F. B."[90] that he had always pursued his profession under the conviction that the spiritual and practical physician were inseparable. "At the risk of being sometimes deemed intrusive, he never failed, when he felt it was necessary, to direct the attention of the dying to reliance on the Divine Sacrifice." But it was in the last four or five years of his life that his deep feeling on religion became much intensified. This side of his character and conduct is given at length by Professor Balfour,[29] who writes thus: "About the year 1848–49 symptoms of disease of the heart manifested themselves, and he was compelled soon afterwards to desist from his laborious professional work. The threatenings of ill health at this period seem to have called his thoughts more especially to things of higher moment than mere professional eminence. While he had not neglected religious duties, he had not yet been led to rest in Christ as his all. Failing health appears to have been the means blessed by God in weaning him from worldly honours, and in bringing him to that Saviour in whom alone his soul finally found peace and comfort. During his future career he was a devoted servant of the Lord, and had the glory of his Redeemer in his view." He would not see patients on Sunday unless they were very ill. The morning was spent in the church of his friend and pastor, the Hon. and Rev. Montague Villiers, Rector of Bloomsbury, and the remainder of the day was occupied in the spiritual instruction of his children. As his letters show, Golding Bird became more and more deeply immersed in these

matters. In 1853 he organised a series of religious meetings among his professional brethren in London, and urged strongly the importance of teachers and practitioners using their influence for the spiritual benefit of students. On December 17, 1853, at a meeting held at his house, the Medical Christian Association was founded: it was to be composed of members of the profession and of students. It was the forerunner of an association which exists to-day. The chief of those who worked with him were Gladstone, the chemist, Le Gros Clark, C. H. Moore, A. P. Stewart, H. B. Norman and S. H. Habershon. About the same time there appeared a letter from a medical student in which he mourned over the want of interest taken in the spiritual welfare of medical students. Golding Bird replied [91] with emotion to this letter, advocating the formation of students' Christian Medical Associations and Bible Classes to promote spiritual religion among their members.

All that now remains is to try to get some picture of the thin, frail, delicate man himself. We have seen how he worked as a student, how, after he became a lecturer at Guy's at the juvenile age of twenty-one, he slaved still more desperately at his original work and at his lectures until he came on the staff seven years later. He knew no rest, he took no holidays, except a week or two during each of the last three years; he never went into society. One biographer, speaking of this period, says: "Many a time after a fatiguing day, and when almost exhausted by a long walk home after an evening lecture, has he sat up far into the night, alternately making notes for some of the numerous papers which appeared from his pen, and employing himself with the construction of apparatus and diagrams for his next lecture."

He was a remarkably good lecturer, he had an easy, fluent delivery, a capital choice of words, together with the rare gifts of interesting his audience and making the matter in hand quite clear. These same attainments caused him to be excellent in debate; few could off-hand marshal their facts to greater advantage. But this facility was largely due to the trouble he took to perfect himself in the art of speaking, lecturing and debating. Owen Rees said of him: "Dr. Bird is also known as one of the most accomplished teachers of the day, and has long been followed and admired by a numerous class. His facility and power of communicating knowledge are indeed such as few can hope to rival." His keen ability in handling his facts also showed itself in the many controversial papers he wrote about scientific subjects.

The output of his scientific work was very great; the larger part of it was chemical, and he falls into the group of chemical physicians such as Marcet, Prout and Bence Jones. His was good accurate research, always correct as far as the knowledge of the time permitted, and it is said that none of his critics found his facts to be wrong. As so much has been written recently in these *Reports* on the chemistry of gastric secretion, it is interesting to remember that Golding Bird told us, eighty years ago, that hydrochloric acid was frequently absent in cases of cancer of the stomach.

From all that we can learn he appears to have been an excellent clinical physician; the case of internal strangulation already mentioned points to this, and we are told that his diagnosis was rarely incorrect. A contemporary says: "While you were with him you could not help feeling that you had his undivided attention . . . the amount of pains he took in the investigation was very remarkable." "His amazing memory and fertility of resource, the wonderful power he possessed of gaining and keeping the confidence of his patients, together with his native mental powers, carried everything before him." He was an exceedingly popular physician in private practice. He had little or no means at the beginning of his career, but, by the time he was twenty-eight, he was earning a thousand a year, and, immediately before his retirement, nearly six thousand a year, having one of the largest practices in the kingdom. He lived at 44 Seymour Street, Euston Square, from 1832 till 1836, when, on the advice of his friends, he determined to practise as a physician, and went to live in Wilmington Square, Clerkenwell, but he soon took a small house in Myddleton Square, near Sadlers Wells Theatre. One of his friends writes: "For many years he lived in an out-of-the-way small square, and in a style that would have greatly interfered with the success of any other man who was looking to a leading practice as a consulting physician. In spite of all these untoward circumstances, success followed him. By his abilities, acquirements and perseverance he overcame all difficulties, and rapidly increased in fame and wealth." By 1850 the house in Myddleton Square, where he had lived nine years, was far too small for his practice and for his increasing family, so in September of that year he moved to 48 Russell Square, in which house he continued to practise until his retirement in June 1854, when he went to live at St. Cuthbert's, Tunbridge Wells, where he died. In Myddleton Square and even in Russell Square, when his health was impaired, if not actually ill, he was never in bed till the small hours of the

morning, and occasionally he even worked in his study all night, but he was always in his consulting-room by nine a.m., where he began the day's work by seeing poor patients gratuitously for an hour.

On March 8, 1842, he married Mary Brett, the sister of his friend before mentioned. There were five children, two girls, both now dead, and three sons, of whom the eldest is now over eighty and lives in Canada; the youngest was ordained, but is now retired. The middle one, the fourth child, was named Cuthbert Hilton Golding-Bird. He is consulting surgeon to Guy's Hospital and I am indebted to him for the information about the family. Dr. Golding Bird's widow founded at Guy's Hospital, in memory of her husband, the Golding Bird Gold Medal and Scholarship for Bacteriology.

This memoir has made it clear that Golding Bird was a man who, although far from robust, habitually overtaxed his strength. He was therefore ill fitted to withstand severe illness. Whether he had had acute rheumatism in youth is not certain, but he suffered from it about the year 1836, and he certainly had a severe attack in the autumn of 1851, soon after moving to Russell Square. This compelled him to stay in bed, a thing he had not done for many years. In this illness he complained of pain down the left arm, so acute that morphia was necessary. During the remaining three years of his life he had to go away a good deal. We know he went to Torquay, the Isle of Wight and Tenby at least twice. Descriptions of his visits to Torquay and Tenby will be found in Professor Balfour's memoir. He went to Tenby after the illness in the autumn of 1851. The Professor gives a long account which appears to apply to a second visit to Tenby in 1853. He tells of the enthusiasm with which Golding Bird explored the caves there for marine animals and plants, and the knowledge of them which he displayed. We learn that "the prestige of a London Hospital Physician had preceded him, and he was pestered with applications from all classes to see and prescribe for them. One morning, when I called on him, I found him sighing over seventeen or eighteen letters from would-be patients. Though resolutely declining to see any who were not introduced to him by the wish of their ordinary medical attendant, he was most kind and patient when they came in this form. . . . With a delicacy which I thought over-stretched he declined all fees. During his six weeks at Tenby his enjoyment was that of a child." From the same book we see how much physicians were, in those days, a slave to clothes. We are told that Golding

Bird, when at Tenby, said in a very emphatic manner: "'How I envy Dr. D. his power of casting off the etiquette of professional costume; I dare not do it to the same extent. I have ventured this summer on some degree of licence. . . . What I do this year is to indulge till about noon in the *négligé* attire in which you now see me' (pointing to a black wide-awake hat, and a very sedately cut black coat, provided with large pockets); 'now, however, I must hurry away. . . . I should lose caste for ever were I detected in this unprofessional costume.'"

It is probable that he had had valvular endocarditis for several years, and that this had been in part at least the cause of his poor health. More definite symptoms showed themselves in the years 1848 and 1849; it was no doubt due to this that he had an attack of hæmoptysis one evening when walking home from Guy's. His illness of 1851 seems to have led to fresh endocarditis and anginal pain. He was still ill when, late in 1851, he returned from his first holiday after this severe illness. In consequence of his poor health the Treasurer relieved him of the duty of seeing out-patients, but this did not mean more leisure, for his private practice was now very large; indeed there were many days on which he could not possibly see all those who desired his advice. About Christmas 1853 his health became frequently interrupted by varying attacks of illness; he had palpitation and an irregular pulse. He asked his friends Addison, Gull and Birkett, with his brother, Dr. F. Bird, to examine him. They were all concurrent in the opinion that he had aortic regurgitation. He followed their advice that he should resign all public appointments; thus he ceased to be assistant physician, without ever having become full physician, to Guy's Hospital. He did not at once give up his large private practice, but, in spite of holidays at Bonchurch in the Isle of Wight in March 1854, by June his health had so deteriorated that it was imperative that he should retire altogether. He bought a small property, St. Cuthbert's, Tunbridge Wells. While the house there was being repaired, he went to Hastings, and here for a few weeks, being too feeble to take outdoor exercise, he sat by the sea on fine days. As soon as practicable he went to Tunbridge Wells, where he rested and took daily drives. He improved a little, so that he could see a few old patients; again he became weak, nausea, vomiting and œdema of the feet supervened, he had much renal pain, the urine contained both blood and pus, the cause of these last symptoms being probably a renal calculus. His brother, Dr. F. Bird, was summoned by telegram, but the patient got weaker and weaker, passing away on October 27, 1854. A few days after he was buried in the Tun-

bridge Wells Cemetery. The front of his tombstone has on it the simple inscription

DOCTOR GOLDING BIRD
Aged 39
Died, 27 October, 1854

Few, if any, physicians have, by this age, attained the position reached by Golding Bird.

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FIVE CASES OF ERYTHRÆMIA

WITH A NOTE ON TREATMENT WITH PHENYLHYDRAZINE HYDROCHLORIDE

By J. A. RYLE, M.D., Assistant Physician to Guy's Hospital.

THE subject of erythræmia, or polycythæmia vera (Vaquez-Osler disease), has been so fully and recently reviewed in Parkes Weber's monograph [1] that it might seem superfluous to record the clinical findings in a further brief series. A personal experience of five cases; the occurrence in three of these of organic gastric complications; some interesting neurological symptoms and a complete post-mortem examination in a fourth; and, finally, the opportunity of studying the therapeutic effect of phenylhydrazine hydrochloride in one case, must stand as justification for the present paper. The cases are described in the order in which they came to my notice. Cases 1 and 2 were shown at the Clinical and Medical Sections and have been previously described in the Proceedings of the Royal Society of Medicine (Vol. XV. Clinical Section, p. 28; and Vol. XVI. Section of Medicine, p. 83).

Case 1. *Erythræmia with Duodenal Ulcer*

A.P., male, aged 47, was admitted to Guy's Hospital on April 24, 1922, for symptoms suggesting duodenal ulcer. Family history unimportant. Personal history:—At the age of nine patient had "congestion of the kidneys." At the age of twenty-six, when in South Africa, he had "slow continuous fever." He had spent three years of his life in South Africa and three years in India, but is not aware that he had any tropical infection. He has suffered on and off since the South African campaign from "indigestion" and "heartburn." He noticed no unusual change in his complexion until after his return from India in 1908. His digestive symptoms on admission are characterised by epigastric pain which comes on two hours after meals, with some relief upon taking food. Eating meat, smoking, and cold weather aggravate the pain. He has never had hæmatemesis or melæna.

The only subjective symptoms referable to his erythræmia are "poor circulation in the extremities" and occasional headaches and dizziness.

Physical features:—Apart from the characteristic colour of the face, which becomes very much more blue on stooping,

there is a remarkable velvety redness of the palatal, faucial and pharyngeal mucosa; there is also distension, with deep purple coloration, of the retinal veins, and enlargement of the spleen. There is very pronounced varicosity of the veins of the legs. Blood-pressure 150 systolic and 100 diastolic.

Urine, April 27, 1922:—Specific gravity, 1020; good trace of albumen; some red cells, pus cells and a few hyaline casts. Urobilin and bile pigment present but no icterus noticed. May 3, 1922:—No bile pigment in urine.

Blood Picture

Red cells		8,800,000 per cub. mm.
Hæmoglobin		136 per cent.
Colour index		0·8
Differential count:	Polymorphs	73 per cent.
	Lymphocytes	23 ,, ,,
	Eosinophils	2 ,, ,,
	Hyalines	2 ,, ,,

Platelets, very large. Blood Group: Group 2.
Fragility of red cells—slight hæmolysis at 0·48 per cent. NaCl (normal).
Clotting time: 1 minute 55 seconds.
Serum, May 2, 1922, shows no bile pigment.
Wassermann reaction: Positive.
Stools:—Tests for occult blood positive.
Fractional test-meal:—Normal type of curve with rapid emptying.
X-ray of stomach and duodenum shows no abnormality except for very active peristalsis at the pyloric end.
Radiogram of thorax shows definitely increased root-shadows.

The Wassermann reaction and x-ray examination of the chest were performed with a view to deciding whether a diagnosis of Ayerza's syndrome* should be considered. The general features of the case, however, and the absence of respiratory embarrassment would seem to place it in the group referred to as primary erythræmia, polycythæmia vera, or Vaquez-Osler disease. The gastric symptoms all disappeared on ulcer diet, with olive oil and belladonna.

An attempt was made recently to trace the whereabouts of this patient with a view to proposing a trial of the phenyl-hydrazine treatment, but no answer was received to my inquiries.

Case 2. *Erythræmia with Cerebral Hæmorrhage*

S.W., male, aged 48, admitted to Guy's Hospital on January 18, 1923; had been under the care of Dr. J. A. Butler, and was transferred to hospital for further observation. Dr.

* Chronic cyanosis with dyspnœa and erythræmia secondary to syphilitic disease of the pulmonary arteries.

Butler reported red cells up to 12,000,000. Patient's main complaint was of "numbness of the left arm, leg, and also of the lips." Family history unimportant. Personal history:—Pyorrhœa three years ago. "Gastritis" two years ago. At the beginning of November 1922, patient suddenly experienced a sensation of numbness in the lips which extended down the left arm and leg; at the same time the hand and foot of the same side began to tingle. Attacks of this numbness were intermittent and came on every three or four hours. On attempting to walk, patient found that he staggered slightly and felt as though he was "walking on rubber." After a time he was compelled to give up work, as his gait was so much affected. Since the onset of these symptoms he has frequently suffered from headaches localised over the frontal region, and at the same time his eyes have ached. At times his sight has been impaired and objects about him have appeared misty and blurred.

On admission:—Patient presents all the features characteristic of erythræmia, *e.g.* excessively red facies, with a slight tinge of cyanosis of lips and finger-tips; extremely injected appearance of fauces and mucous membranes, suggesting some acute inflammation; enlargement of the spleen; albuminuria (·06 per cent.); engorgement of the retinal veins, which are of a "blackberry" hue; and, in addition to these, the neurological symptoms already referred to and more fully discussed hereunder.

Blood Picture

Red cells		9,800,000 per cub. mm.
Hæmoglobin		110 per cent.
Colour index		0·5
White cells		18,750 per cub. mm.
Differential count:	Polymorphs	64 per cent.
	Large lymphocytes	10 ,, ,,
	Small lymphocytes	21 ,, ,,
	Eosinophils	4 ,, ,,

Coagulation time: Normal.
Fragility of red cells: Normal.
Mean diameter of red cells: Less than normal (as 6·4 to 7·2).
Wassermann reaction: Negative.

Radiograms of chest showed a normal heart shadow; increased striation and some patchy opacities in both lungs; but nothing to indicate enlargement or atheroma of pulmonary or other great vessels.

Nervous system:—Patient walks with a distinct limp. There is a persistent numbness in the lips and left leg and arm, with a sensation of tingling in the foot and hand which he describes as resembling "pins and needles." On one occasion he had a feeling of numbness in the left side of the nose which

made it feel as if it was "running." Loss of tactile sensation was noted over areas of the left leg, arm and hand. Tendon reflexes slightly increased. Symptoms rather more pronounced after a bad headache.

Note by Dr. C. P. Symonds.—"On rough examination of the visual fields there appears to be a homonymous defect in the left superior quadrants. I find sensory loss (left-sided) of a type which would correspond with a subthalamic lesion, together with slightly increased tendon jerks, abdominal reflexes much diminished as compared with the other side, and an indefinitely extensor plantar. This points to a lesion of the sensory pathway just below the right thalamus, cutting into the optic radiation. I take it this was a hæmorrhage."

Patient's progress in hospital was uneventful, with the exception that he developed over the lower part of the abdomen and upper part of the right leg some tender reddish patches suggesting subcutaneous hæmorrhages.

A venesection produced slight temporary improvement in his subjective symptoms and a fall in the red-cell count to 7,000,000 per cub. mm.

Dr. Butler reported that the patient remained in very indifferent health after his discharge from hospital and that he was incapacitated for work during the ensuing eighteen months. He was re-admitted to Guy's Hospital on February 11, 1924, in a stuporose condition, rapidly became comatose, and there was uncontrolled voiding of fæces and urine. Knee-jerks were much exaggerated. Babinski's sign present on both sides. Pupils small but not "pin point." He had a bilateral spastic paralysis. Blood-pressure 165. Red count 10,700,000. Hæmoglobin 149 per cent. The spasticity rapidly disappeared and the limbs became flaccid. His pulse rose to 150 and temperature to 101·8, and he died at 6.10 p.m. on the day following admission.

Post-mortem Findings

Brain :—Large hæmorrhage beneath the arachnoid all over the right hemisphere and the upper surface of cerebellum. Signs of old localised hæmorrhage in the right thalamic region.

Lungs :—Deeply congested. Adhesions between pleura and pericardium. Both lungs contain much black blood.

Heart :—Left ventricle much hypertrophied and on section shows two or three white fibrotic patches.

Pulmonary Arteries :—Normal at their origin; all vessels distended with clotted blood.

Aorta :—At the junction of the ascending portion and the arch there is an atheromatous ulcer about one inch in length and half an inch in breadth; adherent to it is a forest of thrombi.

Abdominal Aorta :—Shows moderate atheroma.

Abdominal Viscera :—Congested and contain a little altered blood.

Spleen :—Enlarged to about six times its normal size.

Tough, adherent to surrounding structures. Contains scars of old infarcts.

Kidneys:—Congested. Capsules do not strip readily.

Bone Marrow:—Deep maroon colour.

Case 3. *Erythræmia with great Splenomegaly*

Mrs. T., aged 70, a Belgian widow, seen in consultation with Dr. J. A. Butler, on Feb 2, 1923. In 1921 patient had influenza and bronchitis and was very ill. Later, in 1922, it was noticed that she had a very large spleen. Dr. Butler examined her blood and found that she had 9,000,000 red cells and about 20,000 white cells per cub. mm. Since this time she has been generally unfit, but has complained of no special symptom. Apparently at one time there were bad headaches, and also the skin of the hands was very red, but she has never shown the typical facies of polycythæmia. Urine from time to time contained a little albumen. A more recent count of the blood showed very similar findings. Quite recently patient's left leg became swollen and œdematous and she was kept in bed for several weeks. She is thin and rather wizened, but looks neither polycythæmic nor anæmic. Tongue clean and normal in appearance, but was at one time reported to appear abnormally smooth. There is now only slight œdema of the left leg and none of the right; there is no œdema of the back, no respiratory embarrassment or cyanosis. Heart and lungs normal. The spleen is enormously enlarged, its edge extending across the middle line and its lower limit being lost in the pelvis; it is smooth and apparently gives rise to no pain. Appetite and digestion are fairly good. K.J. present; plantar reflexes flexor. Retinal veins distinctly wider than normal and slightly bluish in colour. Palate and pharynx normal in colour. Blood-pressure 130–90 mm. Fingers of right hand slightly clubbed.

Blood Examination

Red cells	7,000,000 per cub. mm.
Hæmoglobin	102 per cent.
Colour index	0·7
White cells	20,000 per cub. mm.

Film shows no abnormalities of the red cells; nearly all the white cells are polymorphs, *e.g.* in 100 cells, 91 per cent. polymorphs, 8 per cent. lymphocytes, hyalines 1 per cent., eosinophils 0.

Dr. Butler reported her death on March 24, 1925. Her hæmoglobin had remained at 100 per cent. or thereabouts, red cells at 6,000,000 per cub. mm. Except for increasing dropsy and a terminal gangrene of the finger-tips no new symptoms developed, but Dr. Butler mentioned that some tendency to fever

and sweats was noticed after a course of radium-therapy to the spleen. The other common causes of great splenomegaly in this country—namely, splenic anæmia and splenomedullary leukæmia —can clearly be excluded in this case. I must admit, however, that the degree of erythræmia and the facial appearances were less striking than in the other four cases of this series. Also the distension of the retinal veins, which I regard as a valuable diagnostic sign, and of which Sir William Hale White[2] has written: "It seemed to me the appearance was such that I should recognise it again as characteristic of the disease, and in this my ophthalmic colleague, Mr. H. L. Eason, agreed with me," was less conspicuous. Redness of the hands and sweating are both mentioned as occasional symptoms in erythræmia, and the high polymorphonuclear count is characteristic.

Case 4. *Erythræmia with Gastric Ulcer*

W.R., male, aged 62. I was asked to see this patient by Dr. W. O'Brien on May 23, 1924, on account of digestive symptoms. Patient had pain coming on one hour after food and eased by taking food and lying down. Family history:—Father died of asthma, mother of heart disease. One brother "dyspeptic." Has seven healthy children. Has had no other serious illness himself.

Patient has the typical facies of polycythæmia, but at the same time looks pinched and cachectic. Teeth and gums very unhealthy. He is wasted, the bony points, and especially the iliac crests, being very prominent. There is much splashing on palpation of the stomach 2½ hours after a breakfast of tea and egg. I queried a tumour in the left upper quadrant. (Later I decided that this must have been the enlarged spleen.) Rectal examination negative, no glands above the clavicle. Radial arteries thick. Blood-pressure 145 systolic, 100 diastolic. Retinal vessels the colour of blackberry juice. A trace of albumen. Hæmoglobin 120 per cent.

Two days after seeing me, patient had a big coffee-ground vomit, and was in bed for four or five days. The pain left him three days later and there was no recurrence. His septic teeth were extracted and his weight increased from 8 st. 7 lbs. to 9 st. 4 lbs. He was investigated in hospital in August 1924, when x-ray and test-meal examinations confirmed the diagnosis of an ulcer in the pre-pyloric region. He was ordered appropriate treatment.

In response to subsequent enquiries I received the following reply from Dr. O'Brien on March 11, 1925:—"He made a good recovery and I have not seen him for some months. His daughter told me to-day that he is keeping fit so long as he is not rash with his diet. He has no troublesome symptoms referable to his polycythæmia at present." Phenylhydrazine treatment was therefore not advised.

Case 5. *Erythræmia with Gastric Hæmorrhage*

Mrs. B., aged 42. I was asked to see this patient by Dr. E. Hardenberg on January 6, 1925, on account of a recent hæmatemesis. Excepting for very occasional " bilious attacks," patient has enjoyed fairly good health until nine weeks ago. Then one day she had some giddiness and headache and later in the day vomiting, which continued until one o'clock in the morning. The vomit at first contained food and later was " bilious " and " brownish in colour." A few days later she had another attack and brought up " perhaps a cupful " of more or less pure blood. She has had great flatulence with noisy eructations. A week ago she again had headache, flatulence and vomiting, with specks of blood in the vomit. The headaches have been rather more over one eye than elsewhere. She has spent a fortnight in bed on a light diet, but not a strict ulcer diet. Since the attacks started there has been constipation. Appetite good; bowels regular; always has cold feet and hands. Has always been very spare but weight does not vary much; has lost a little weight in the attacks, and now weighs 8 st. 10 lbs., her average being 9 st. No urinary symptoms. Periods formerly regular, now more frequent. Sleep good. Mother died of cancer; no other familial disease. Leads a healthy life and does a lot of work in her garden. A few years ago was a vegetarian for eighteen months and felt much better, but later returned to an ordinary diet. Has always had a very high colour. Patient is tall and very lean and has the typical appearance of polycythæmia. Cheeks brick red with a faint tinge of purple; lips a more definite tinge of purple. Conjunctivæ and other mucous surfaces redder than normal. Very little superficial fat. Retinal veins wide and purplish. Chronic mastitis in both breasts and a small cyst in left breast. Glands in both axillæ slightly enlarged but easily movable. Abdominal examination shows the spleen margin to be one hand's-breadth below the costal margin, but the spleen feels unduly mobile, and is probably low in position. Nothing else abnormal to be felt, and no tenderness. No signs of cardiovascular or pulmonary disease. Blood-pressure 150–90 mm. Urine normal. Hæmoglobin 108 per cent.

A hæmoglobin-free diet was prescribed and the stools were tested for occult blood. A negative report being obtained she was gradually promoted to a post-ulcer régime, and, as she had previously felt the better for it, was advised to plan her diet on vegetarian lines.

Treatment with Phenylhydrazine

At about this time my attention was drawn by Professor Adrian Stokes to a paper by Trevor Owen [3] in the Johns Hopkins Bulletin reporting favourable results with phenylhydrazine hydrochloride in a case of polycythæmia. Trevor Owen, sup-

porting the general view that the disease depends upon a great over-activity of the bone marrow, points out that "treatment may either aim to depress the bone marrow or to increase the rate of blood destruction." X-ray treatment to the long bones has been employed for its effect on the marrow with varying success. Morawitz and Pratt [4] had used phenylhydrazine hydrochloride in 1908 to produce experimental anæmia in animals. Taschenberg [5] employed phenylhydrazine hydrochloride in a case of erythræmia with splenomegaly in 1921 and recorded a marked fall in the blood-counts, but he found it necessary to employ larger doses each time the symptoms recurred. Trevor Owen's patient was given 0·1 grm. of phenylhydrazine hydrochloride in a capsule every day, increasing to a dose of 0·2 grm. on four occasions only. A dose was given every day for sixteen days, and then 0·1 grm. every other day for four doses. In a period of about five weeks the hæmoglobin fell from 145 per cent. to 72 per cent., and the red cells from 7,612,000 to 3,176,000 per cub. mm. There were no unpleasant subjective symptoms. The only complications were a phlebitis of the internal saphenous vein and a transient hæmaturia. Symptoms began to recur in two months, when a short course of 10 doses of 0·1 grm. quickly brought the hæmoglobin figure back to 90 per cent. and red cells to 4,640,000 per cub. mm. Trevor Owen regards the action of phenylhydrazine as being mainly one of blood destruction. He claims that the drug has an advantage over benzol in that it has a selective action on the red cells, whereas benzol may cause a serious leucopenia.

Case 5 of the present series was treated with doses of 0·1 grm. daily. On April 20, 1925, after a three weeks' course, the subjective symptoms were all relieved, and Dr. E. Billing reported the results of his blood examinations during this period as follows:

1st	Examination:	Hbg. 116 per cent.	Red cells 6,000,000 per cub. mm.
2nd	,,	Hbg. 112 per cent.	
3rd	,,	Hbg. 110 per cent.	
4th	,,	Hbg. 105 per cent.	
5th	,,	Hbg. 90 per cent.	(Treatment stopped.)

In July 1925 symptoms were returning again and hæmoglobin had risen to 108 per cent. A further course was given.

I saw the patient on July 31, 1925, and she expressed herself as having felt very much better for her treatment until two or three weeks ago, when she was again bothered with "tight feelings" in the head and vague anxieties. There has been no

return of digestive symptoms. Physical appearance as before. No complications or unpleasant symptoms recorded.

Hæmoglobin . . .	100 per cent.
Red cells . . .	6,600,000 per cub. mm.
White cells . . .	16,200 per cub. mm.

Following a third course of treatment the hæmoglobin fell to 90 per cent. on August 21, but had risen again to 110 per cent. on October 20, when treatment was started again. On November 3 the hæmoglobin was 102 per cent., and on November 11, 95 per cent.

Dr. Billing reports that even when the hæmoglobin is down to 90 per cent. the crimson appearance of the face remains. Patient states that she thinks that her condition "remains stationary for some weeks after the cessation of treatment and then suddenly gets bad again."

Discussion

Five cases of erythræmia have been described. It is noteworthy that three of these presented themselves on account of gastric symptoms pointing to a breach of the gastric or duodenal mucosa. In two cases there was contributory evidence of a chronic ulcer. In the third case presumption favoured a more acute lesion of the gastric mucosa, possibly a rupture of an over-distended vein. In the long series to which he refers, Parkes Weber only quotes two cases of gastric ulcer, both discovered in the course of a post-mortem examination, but gastric hæmorrhage is mentioned as an occasional symptom. Hale White [2] attributes the gastric symptoms of one of his patients, who gave a history of probable hæmatemesis, to splanchnic engorgement. One case (Case 2) in my series presented himself on account of neurological symptoms, correctly attributed to a local vascular lesion in the right thalamic region. Death was due to an extensive sub-arachnoid hæmorrhage. One case (Case 3) showed a degree of splenomegaly unusual in this disease. One patient was treated with courses of phenylhydrazine hydrochloride in doses of 0·1 grm. daily and on each occasion showed improvement in subjective symptoms and a very definite reduction in the hæmoglobin figures. Dr. G. H. Hunt tells me that a case which he treated with this method, so far from showing improvement in symptoms, felt less well and the treatment had to be discontinued.* The improvement obtained in Trevor Owen's case and in Case 5 of this series suggests, however, that the treatment should be worthy of a further trial in selected cases. It should only be carried out

* This case is described on p. 92.

under careful control, with frequent hæmoglobin estimations and, where possible, with complete blood-counts.

I am indebted to Dr. J. A. Butler, Dr. W. O'Brien, and to Dr. E. Hardenberg and Dr. E. Billing for their courtesy in allowing me to refer to these cases and also for valuable co-operation in their investigation and treatment.

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CONGENITAL CYSTIC DISEASE OF THE KIDNEYS, LIVER AND PANCREAS

By W. GORDON SEARS, M.B., Out-patient Officer, Guy's Hospital.

CONGENITAL cystic disease of the kidneys is a well-known, but unusual condition. Its association with cysts in the liver and the pancreas is referred to by various writers, but I have not been able to find in the literature the description of any actual case. The following case seems therefore to be worthy of record.

P. S., male, aged 44, was admitted into Stephen ward on May 31, 1925, under Dr. A. P. Beddard, to whom I am indebted for permission to publish this record. He was taken in for enlargement of the abdomen and vomiting. There is no family history of this condition, but an accurate account was not obtainable. He himself had never before had any serious illness. He was a fairly heavy drinker.

He stated that he was quite well until ten months before, when he noticed swelling of the abdomen and increasing lassitude and loss of energy. Recently he had had to get up once during the night to pass urine. Two days before admission he became somewhat collapsed and suffered with nausea and vomiting and he was constipated. His temperature varied between 98° and 102°, and his pulse between 76 and 100. He was vomiting five or six times a day.

On examination nothing abnormal was found in the cardio-vascular or respiratory systems. His blood pressure was 150 mm. systolic, and 100 mm. diastolic. His central nervous system appeared normal. His right pupil was irregular owing to a coloboma iridis, which he stated had been present all his life. The optic discs were normal.

His abdomen was considerably distended and difficult to palpate. There was dullness in both loins and some fluid was thought to be present. The liver was enlarged and its lower border was one inch above the umbilicus in the right mid-Poupart line. The surface felt slightly irregular. There was a large tumour in the left loin, at first thought to be the spleen, but later considered to be connected with the kidney. Subsequently a tumour was felt in the right loin, which with some difficulty could be made out as a structure separate from the liver, and was the right kidney.

His Wassermann reaction was negative. A blood count showed :

Red cells	3,750,000 per cub. mm.
Hæmoglobin . . .	70 per cent.
White cells . . .	7,200 per cub. mm.

Differential count :

Polymorphonuclear cells .	75 per cent.
Lymphocytes . . .	13 ,,
Hyaline cells . . .	12 ,,

A blood urea estimation (5.6.25) showed 3·9 g. of urea per 1000 c.c., or thirteen times normal.

Urine : sp. gr. 1010–1020; albumen present, 2–4 parts per 1000. No sugar. Microscopical examination showed the presence of red cells and pus cells in fairly large numbers. A few bacteria were seen. No casts were detected. The urine was red in colour for two days before death, and the patient was passing an average of 30 ounces in 24 hours. Shortly before death 25 ounces were withdrawn with a catheter. This obviously contained much blood and pus.

The vomiting appeared to improve somewhat with treatment, but he became weaker and confused mentally. Towards the end he showed uræmic twitchings, and died on May 8 from uræmia.

Autopsy

Cardiovascular system :—Normal. No marked hypertrophy of heart.

Respiratory system :—Lungs congested, otherwise normal.

Alimentary system :—

Liver.—This was considerably enlarged and contained many cysts, which varied in size from that of a large walnut to a pin's head (Fig. 1). The cysts were scattered throughout the substance of the organ and contained clear fluid. The portions of the liver between the cysts appeared normal. The biliary passages were normal.

Pancreas.—There were some small cysts on the surface of the pancreas and a few in its interior, but these attained no greater magnitude than that of a large pin's head.

Spleen.—No cysts were seen.

Urinary System :—

Kidneys.—Both kidneys were transformed into large multi-cystic masses (Fig. 2); the left being somewhat larger than the right, and measuring about 13 inches in length. The combined weight of the kidneys was about 4000 g.

There was no obvious normal renal tissue left.

The ureters were patent.

The bladder was inflamed.

There were no other abnormal findings.

FIG. 1.
Liver of case recorded (R. C. Brock).

FIG. 2.
Kidneys of case recorded (R. C. Brock).

Microscopical Appearances

1. *Kidney.*—There was a considerable excess of loose fibrous tissue throughout the whole section. There were some normal glomeruli and tubules. Some fibrotic glomeruli and dilated tubules were present. There were a number of cystic spaces of varying size lined by a single layer of cubical epithelium and surrounded by fibrous tissue without any definite basement membrane (Fig. 3). Some of the cysts showed evidence of inflammation with polymorphonuclear infiltration in their

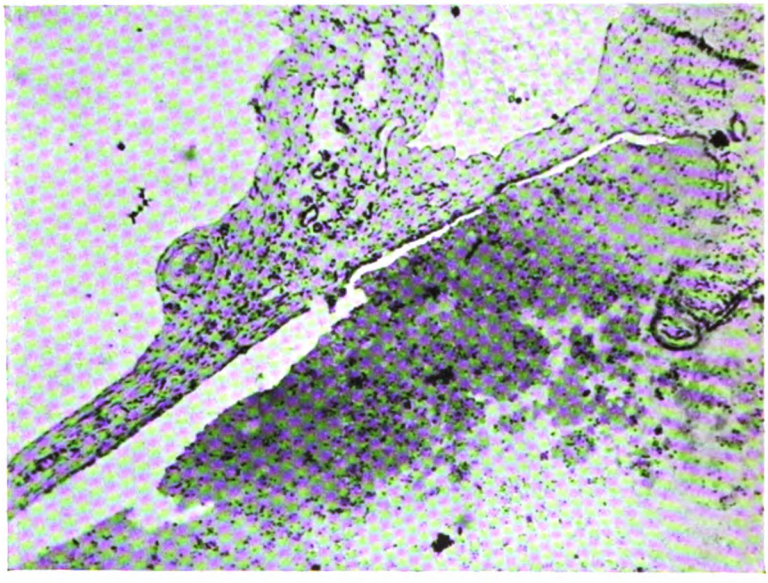

Fig. 3.

Wall of cyst in kidney (J. W. Shackle).

neighbourhood, and they contained necrotic material. In patches there was a small round-celled infiltration of the connective tissue which was most marked in the region of the cysts. The arteries were thickened and their lumen narrowed, giving the appearance of arterio-sclerosis.

2. *Liver.*—There was no general increase in connective tissue throughout the liver nor in the portal spaces. The fibrous tissue was limited to the region of the cysts. There was no evidence of any biliary cirrhosis. A number of cysts were seen. The smaller ones were lined with flattened epithelium (Fig. 4), but in the larger ones this was lost and they had a fibrous tissue wall. The liver substance itself looked normal except in

the vicinity of the cysts, where the cells showed evidence of degeneration and the lobules were distorted. The nuclei of the liver cells near a cyst were smaller and did not stain so well as those of normal liver cells. In one place there were some small cystic spaces lined with low epithelium and surrounded by connective tissue, lying approximately in the position of Glisson's capsule, but there were no blood vessels near them. No definite communication between the cysts and the bile ducts could be made out.

3. *Pancreas.*—Mostly normal pancreas was seen in the section. Some of the ducts appeared to be dilated. There was a large cyst which was loculated and lined with a flattened epithelium (Fig. 5), but the latter was absent in places. The cyst was surrounded by a small amount of connective tissue separating it from normal pancreas.

The islets of Langerhans were normal.

There was no excess of fibrous tissue throughout the organ.

Historical Note

One of the first reported cases of cystic disease was that of Alexis Littré [1] (1658–1725), occurring in a full-term fœtus.

"In a fat and large fœtus all the parts were healthy and well-formed except the kidneys. This infant died in the belly of his mother during labour, which was long and difficult. The two kidneys, much larger than normal, resembled a bunch of grapes, that is to say, they appeared to be composed of membranous vesicles of different sizes, round or oval in shape, arranged one against the other and full of a watery-looking fluid, a little dense and having a uriniferous odour. The ureters were patent."

The first case reported in this country of cystic disease of the kidneys associated with a similar condition of the liver was that of Bristowe [2] in 1856. Wilks showed specimens from the Guy's Hospital Museum about the same time. They offered no explanation of the pathology of the condition.

It is difficult to deal with the literature of this subject and with the theories which have been put forward to explain the condition, owing to the fact that few writers appear to realise that both organs may be involved. They write on "cystic disease of the kidneys" or "cystic disease of the liver," and offer their explanations for the individual conditions without an attempt to correlate the two. However, the comparative frequency with which they occur together is surely more than

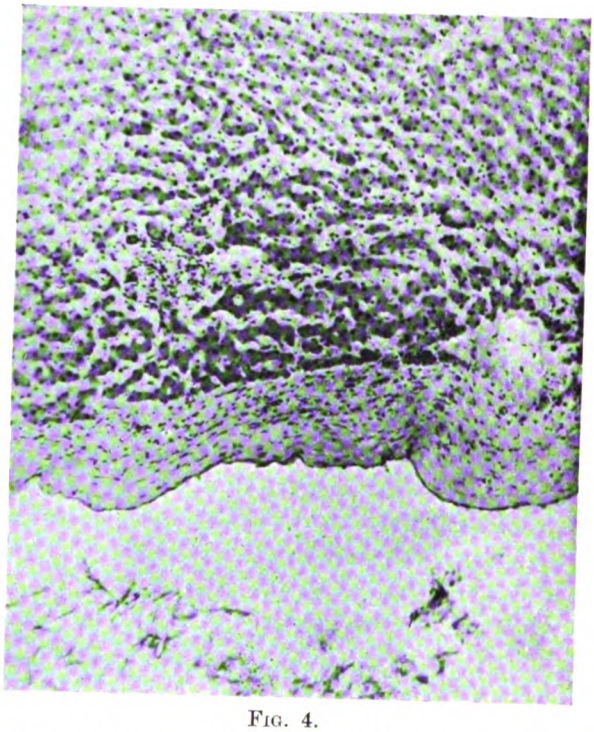

FIG. 4.

Wall of cyst in liver showing flattened epithelium (J. W. Shackle).

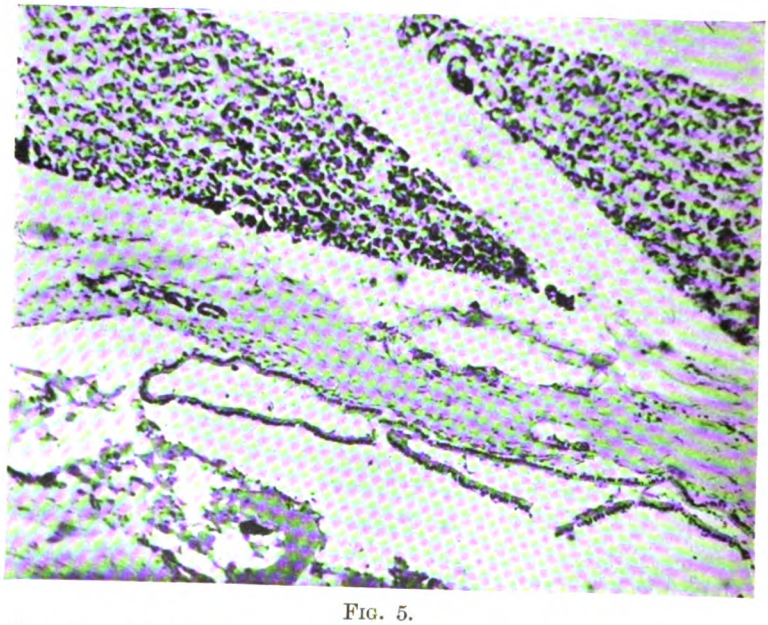

FIG. 5.

Wall of cyst in pancreas lined with columnar epithelium (J. W. Shackle).

coincident, and there must be some common factor in their pathology.

The Clinical Manifestations of the Disease

As a general rule congenital cystic disease is only seen at two periods of life:

I. In the fœtus and young infant.

II. In the adult over forty years of age.

I. *In the fœtus and young infant.*—Shattock [3] records the case of a four-months male fœtus, in which both kidneys were cystic and presented the typical appearance of congenital cystic kidneys. The urethra, however, was imperforate and the bladder and ureters distended. There were no other abnormalities in this fœtus. He also records a case [4] of a full-time fœtus in which both kidneys were cystic. There were no cysts in the liver, and the ureter and other organs were normal. Still [5] describes the case of a female infant of seven weeks in whom both kidneys and the liver were cystic; she had died with uræmic symptoms. He quotes a case of Rolleston's occurring in a still-born infant; this child had webbed toes, six fingers on one hand and an occipital meningocele; there were cysts in the liver and both kidneys were cystic.

Meader [6] examined carefully serial sections of the kidneys of a still-born male fœtus, one of twins, the other being a female which survived. This fœtus had cysts in the liver and the left kidney. The right was hydronephrotic and was associated with stenosis of the right ureter a few centimetres above the bladder. The left ureter was patent. The hands were deformed, there were accessory fingers; the feet were clubbed, the left possessed six toes and the right seven. There was a meningocele projecting from the posterior fontanelle.

Blackburn [7] in an excellent paper on cystic disease of the kidneys and liver mentions the condition occurring in a monster born at full term. The kidneys were enlarged and cystic. The liver contained no macroscopic cysts, but under the microscope numbers were discovered. This monster was hydrocephalic and perforation was necessary in order to effect delivery. The mother was apparently healthy, but had given birth two years previously to another monster with a hydrencephalocele necessitating embryotomy. This fœtus also had cystic disease of both kidneys.

Rolleston,[8] writing in 1904 on cystic disease of the liver, says that it is very probable that those cases seen in adult life are also congenital, but, being less marked, have survived. At that time there were only about fifteen published cases of

the condition occurring in new-born infants. He points out that the condition may not be recognised unless the liver is examined microscopically. There is a frequent association of polydactylism, and he thinks that if the livers of all monsters were examined microscopically, cystic disease might be found more frequently. Real cystic disease of the liver is practically always associated with a similar and more advanced condition in the kidneys, but he quotes two cases in which the liver alone was affected, recorded by Dudgeon [9] and Batty Shaw.[10] When the condition occurs in infants the liver as a rule is not much enlarged, and rarely are there any macroscopic cysts, but in one case the liver was so large as to impede delivery.

Boinet and Raybaud [1] collected a number of cases of cystic kidneys occurring in infants, and they make the following statements. If the kidneys attain a large size during intra-uterine life they lead to death of the fœtus either from causing premature delivery or rendering delivery impossible. Out of 35 cases, 14 were born at term, 16 at eighth to ninth month, 4 at seventh month and 1 at sixth month. Therefore the condition does not seem to have much influence on the development of pregnancy. Again, in 44 cases where the deformity was marked at term, 12 were normal labours; in 18 labour was difficult, requiring forceps, version, etc., and in 14 embryotomy was necessary. In a collection of 25 cases, 12 were born dead, 10 died soon after delivery from asphyxia, and the rest lived varying periods up to 42 days. In their own case of a male infant one month old, the liver was congested and contained no macroscopic cysts. The right kidney was all cystic: there was no trace of papillæ or calyces, and the lower part of the ureter was a fibrous cord. The upper part of the left kidney was normal, but the lower pole contained cysts. The cysts held an alkaline fluid of high specific gravity, containing 72 parts of urea and 42 parts of phosphoric acid per 1000. There was much albumen, no sugar, and microscopic examination showed coagulated mucus, detached epithelial cells and crystals of magnesium ammonium phosphate.

I have been able to collect 11 cases of the condition occurring in the fœtus and infant from the literature. Of these, 4 were males, 2 females and in 5 the sex was not mentioned. In 4 cases the liver was cystic, in 3 it was stated not to be cystic, but microscopic sections were not cut; in 4 the liver was not mentioned. One was a monster and 6 had other deformities. The condition was bilateral in every case.

II. *In adults.*—The case recorded in this paper presents

many of the typical features of the condition as it occurs in adults, and most of the published cases have similar histories and clinical signs. The vast majority of cases are manifest between the fourth and fifth decades of life, and at first are without appreciable symptoms. There is some fullness and feeling of weight in the abdomen, some polyuria and occasional hæmaturia. The commencement of the disease is very insidious, and a large number of cases have presented no indication of ill-health till shortly before death, which has most often resulted from uræmia. In very many the condition has only been discovered post-mortem. In most of the cases during life the symptoms have been referred to the kidneys. The urine is, as a rule, of low specific gravity and usually contains albumen in small quantities. Pus may be present, but this appears to be due to an associated pyelitis. Hæmaturia is a fairly frequent symptom, and there may be a history of the occasional presence of blood in the urine for as long as twelve years. Ascites may be present. There is some degree of anæmia, and the patient's life usually terminates with uræmic symptoms, which may only supervene shortly before death.

Tumours are felt in one or both loins, and may easily be confused with the spleen or a tumour of another organ. The tumours fill the loin, and if there is no perinephric inflammation can usually be moved about to some extent. They may be rather tender, more so when there is secondary infection; they are fairly firm and have some slight irregularity of surface.

It is sometimes possible to palpate an enlarged liver, the surface of which may feel irregular. On cystoscopy the bladder usually appears normal, unless there is infection of the urinary tract. The blood urea may be raised, particularly at the termination of the disease.

The clinical course of the disease may conveniently be divided into three stages.

(1) *Latent stage.*—There is progressive enlargement of one or both kidneys without other symptoms. This presumably is of very indefinite duration and may be present for many years.

(2) *The stage of renal tumour.*—There may be a dull ache in the loins or no pain at all. Hæmaturia may occur. In other cases a tumour is discovered in one or both loins in the course of an examination, although there have been no renal symptoms, and it is then that the difficulty arises as to whether operative procedures should be adopted; operation being contra-indicated in cystic disease of the kidneys. Later symptoms of decreasing renal function develop, such as nausea, flatulence,

constipation and headache, and there is polyuria of a low specific gravity.

(3) *The stage of uræmia.*—This is usually of short duration and terminates in the death of the patient.

The following table gives some statistics collected from various sources :

Source.	Cases.	Sex.		Age.	Bilateral or Unilateral.	Cysts in Liver.	Remarks.
		Male.	Female.				
Selber (11) . .	198	82	116	40–60	—	—	
	150	—	—	—	Bilateral 140	39	
Luzzato (12) .	226	—	—	—	Bilateral 185	—	
Rolleston (8) .	28	7	21	3 infants 17 over 50 4 over 70			
Le Jars (13) .	69	—	—	—	Unilateral 2	—	
Ritchie (13) .	72	—	—	—	Unilateral 2	—	
Autopsy records Guy's Hospital, 1885–1915	10	6	4	9 over 40 1 aged 10 who died of phthisis	Bilateral 9	3	
Cases collected from literature (including the above Autopsy records)	55	24	31	3 over 60 34 over 40 9 between 10–30	Unilateral 3	Cystic 22 Not cystic 15 No mention of liver 28	Cysts in spleen in 1 case Death stated to be due to uræmia in 17
	11			Infants and fœtuses	Bilateral 11	Cystic 4 Not cystic 3 No mention of liver 4	1 monster 6 with other deformities

The conclusions which may be drawn from this table are that the condition is slightly more common in women than men, although some writers have stated that it occurs in females twice as often as in men. The disease usually proves fatal between the ages of 40 and 60. In only about 10 per cent. of cases is it unilateral. Indeed the figure may be less than this, for in many of the cases recorded as unilateral there has no doubt been no examination for microscopic cysts in the organ. It has been stated that in unilateral cases the left kidney is more commonly affected.

In 30 per cent. of cases of cystic disease of the kidneys the liver is also involved. Luzzato, however, only found 5 cases in 90 (5·5 per cent.) of the combined condition, but most other writers think this association is more frequent. Again, it seems probable that if the liver of every case of cystic disease of the kidneys were examined microscopically, cystic changes would be found in a considerably higher percentage of cases.

The case recorded in this paper is the only one in which cysts in the pancreas are mentioned. Blackburn [7] records a case in which there were cysts in the hilum of the spleen.

The Hereditary Nature of Congenital Cystic Disease

The fact that this disease may occur in several members of the same family has been pointed out by a number of writers. Osler [14] reported the incidence of the disease in five children of one mother. Borelius [15] mentions three cases occurring in one family. Love and Richmond [16] also refer to several occurrences in one family. Crawford [17] produces a family tree in which the disease occurred in at least ten members of the family in two generations traced from a possible case in the preceding generation. He makes quite clear the familial and hereditary nature of the disease and definitely concludes that it is a familial affection. Since the present paper was commenced, Cairns [18] has described a family living in the East End of London in which there was evidence of the occurrence of polycystic disease of the kidneys in three successive generations, with such frequency in the second and third generations as to leave little doubt as to its hereditary origin. He records full descriptions of each of the cases, which give clear clinical pictures of the disease. As this work has been so recently published and is easily accessible, there is no need to do more than mention the main points of his paper. Eight members of the family have had polycystic disease and two others are probably affected. In the first generation one female had the disease; in the second, four males; in the third, two females and one male and possibly two other females. In all cases the diagnosis was made on post-mortem or indisputable clinical and urological findings. In the three generations, including the founder, there were 42 individuals, among whom there are at least 8 cases of polycystic disease; in other words, 19 per cent. of this family suffered from the affection. In three of the cases that came to autopsy there were cysts in the liver. There was no consanguinity in the family. Another interesting point which he makes is that myopia occurred in 21 per cent. of the family, and was therefore probably hereditary in this stock, but myopia and cystic disease appeared to occur independently. This is interesting in view of the frequent occurrence of congenital abnormalities which are so often recorded as being associated with this disease.

He further quotes Bull's [19] case, in which three generations were affected with congenital cystic disease. In all, twenty-three examples of polycystic kidneys were collected from the literature as affecting more than one member of the same family.

In dealing with the transmission of the disease, it is pointed out that males and females are alike affected and that both may transmit the disease when mated with normal individuals, and of their offspring either sex may inherit the condition.

There is no evidence to show whether or not it may be latent for a generation. A table is also given which suggests that there may be a variation in the intensity of the disease in successive generations. The variations are all in the same direction, namely, that the younger generations have their first symptoms and die at an earlier age than the members of former generations affected with the disease.

It is evident, as Cairns points out, that those who would wish to refute the statement that polycystic disease is hereditary in origin must produce extensive genealogical studies of isolated cases of the disease, in which is included evidence from post-mortem as well as from clinical examination, showing that no other cases of this condition had occurred in the family.

It may therefore be concluded that congenital cystic disease is a definitely hereditary condition, although this is not obvious in every case, probably owing to the difficulty in obtaining accurate and detailed family histories, and the fact that the sufferers may die from other causes.

The Association with other Congenital Abnormalities

Another interesting fact about this disease is the frequency of the occurrence of other congenital abnormalities. This is most marked in the cases of the condition occurring in the infant and fœtus. They appear to be less commonly found in the adult cases, possibly because their presence determines the early death of the individual. Numerous abnormalities are recorded; among them are the following.

1. *Associated Lesions of the urinary apparatus.*—The urinary passages are stated to be abnormal in 40 per cent. of the cases occurring in infants (Boinet and Raybaud [1]). Rarely it is associated with congenital hydronephrosis. The calyces or papillæ may be incompletely developed. The ureters may be occluded either as a fibrous cord or as a simple atresia at one point of their course. Recto-vesical fistula has been found. The renal vessels are usually normal but may be atrophied.

2. *Malformation of the genital organs.*—Hypospadias, cryptorchism, partial or total absence of the external genitals and double uterus and vagina have been noticed.

3. *Visceral malformations.*—Besides the occurrence of cysts in the liver, pancreas and spleen, it is stated that the suprarenals are sometimes atrophied or sometimes hypertrophied. Absence of the spleen has been noticed and also imperforate anus. A case has been recorded in which there was inversion of the thoracic organs.

4. *Other abnormalities.*—Meningocele, hydrocephalus, poly-

dactylism, webbed fingers and toes, and club foot are not uncommonly associated with the disease.

Luzzato [12] states that out of 90 cases, 64 (71 per cent.) had other congenital abnormalities, and in 32 of these the errors of development were outside the urinary organs.

It may be mentioned here that Blackburn [7] records a case in which the spleen was large and firm and showed signs of recent perisplenitis on the external surface. On the internal surface about the hilum were numerous small cysts about the size of millet seeds. They seemed superficial and contained clear watery fluid. The specimen was unfortunately lost, so that microscopic examination could not be made.

The Macroscopic Appearances of the Organs

The macroscopic appearances of the kidneys and liver in the case recorded here resemble closely those of other reported cases, and a summary may be made which seems to apply to all cases of the condition.

1. *Kidneys.*

(*a*) The kidneys, although cystic, preserve their reniform shape.

(*b*) The capsule of the kidneys usually strips easily.

(*c*) Cysts may or may not project above the surface of the kidney, so that the organ looks like a bunch of grapes. It may be smooth or a little mammillated, and fœtal lobulation may persist.

(*d*) The kidney is usually a mass of cysts of varying sizes up to that of a tangerine orange. In the smooth type of kidney the cysts are said to be of more uniform size.

(*e*) Little or no normal kidney tissue may be seen, and there is no definite differentiation between cortex and medulla.

(*f*) The contents of the cysts are usually clear or straw-coloured, but in some cases turbid, opalescent and almost solid with albumen. Urea, cholesterin crystals, and altered blood may be present.

(*g*) The kidneys may be anything up to 15 inches in length and 6 or 7 inches in diameter, and may weigh several pounds. The largest one that Blackburn [7] could find reported was a case of Dr. Hare's, in which one kidney measured 15¼ inches long and weighed 16 lbs.

2. *Liver.*—Rolleston [8] states that as a rule in infants the liver is not much enlarged, and that there are rarely any macroscopic cysts, but cases have been recorded in which the liver has been so large as to impede delivery. In adults enlargement

of the liver is the rule, if cystic disease is present. The liver may be greatly increased in size. There is usually much less cystic transformation in the liver than in the kidneys. The cysts are larger in the adult than in the infant, and he suggests that this is probably due to the coalescence of several small cysts. The cysts are scattered throughout the substance of the organ, but they may appear on the surface. They usually contain clear albuminous fluid which is sometimes brown, probably from hæmorrhage. Protein, urea, chlorides, cholesterin, calcium oxalate, leucin and creatin are said to be present, *but not bile.*

Microscopical Changes found in the Kidney

The histological appearances described by most writers on this subject are almost identical, so that a more or less typical account can be given. There are only slight variations in the infant and adult types.

Meader [6] cut serial sections of the kidney of a full-time dead fœtus which was affected with this condition, and he makes out the following points. The cortex was thickened to comprise the bulk of the kidney, and in this case the medullary part was entirely absent. Glomeruli were found near the calyces of the pelvis, which was contiguous with the under surface of the cortex. From the pelvis of the kidney thick partitions of embryonic connective tissue extended towards the surface of the organ.

Cysts.—Occasionally a cyst was found with a glomerular tuft hanging from its lining wall; clearly such a cyst was the dilatation of the capsule of the glomerulus. Frequently dilatation occurred in the first convoluted tubule, while the glomerulus was normal, and connected with the cyst by the proximal part of the tubule. Occasionally there was a relatively small dilatation of the glomerular capsule which was connected by a narrow tubule to a larger dilatation of the first convoluted tubule. There were numerous glomeruli which were not cystic and not connected with cystic tubules, and there was never more than one glomerulus connected with each cyst. The larger cysts had no apparent opening, and contained no glomerular tuft inside.

The walls of the cysts were lined with a single layer of cubical epithelium which was necrotic in parts. The blood vessels were not very numerous, the arteries were quite large and extensively thickened.

In Shattock's case [4] of a full-time fœtus the vessels were healthy, but there was an excess of connective tissue throughout

the organ, which was arranged concentrically round the cysts.

Summary.—Meader found normal glomeruli, glomeruli without uriniferous tubules, glomeruli with dilated capsules but no outlet, glomeruli with short tubules opening into cysts, the glomeruli in these cases being either of normal appearance or having a dilated capsule. Each cyst was only a single associated glomerulus.

Blackburn,[7] in describing fully the appearances of sections of a kidney from a woman of 42, found that there was great increase in the connective tissue of the organ, and that the cortex resembled somewhat the appearance of chronic interstitial nephritis.

Glomeruli.—Many glomeruli appeared healthy, but some were atrophic with shrunken capillary tufts. Some appeared to be becoming cystic, and in these the capsule was dilated and the capillary tuft converted into a homogeneous colloid material which remained unstained except for a few nuclei at the point of attachment, which still retained their vitality.

There was an increase in the connective tissue round the glomeruli, which in some cases appeared as a definite fibrous ring, especially in those cases in which cystic changes were taking place.

Convoluted tubules.—In most cases their epithelium was swollen and granular, and sometimes almost filled their lumen. Some contained colloid casts, and a few appeared to be becoming cystic; in these the epithelium seemed to be proliferating and was several layers thick in places.

Arterioles.—These had thickened walls and were embedded in excess of fibrous tissue.

Medulla.—In the medulla the increase of connective tissue was more marked, and many of the straight tubules were dilated.

Cysts.—These were scattered throughout the cortex and medulla and contained unstained colloid material. They all had a definite fibrous capsule and most had an epithelial lining. In the larger cysts the epithelium was flattened, but in the smaller ones it was sometimes cubical in type. Some of the smaller cysts had septa across them. In some places the epithelial lining was lacking and the connective tissue appeared to encroach on the lumen of the cyst, which in these cases contained granular material with cells present at the edges appearing like a leucocytic infiltration.

In one case described by Cairns [18] the media of the interlobular and arcuate arteries was slightly hypertrophied and the intima was thickened by reduplication of the elastic fibres,

and frequently showed hyaline degeneration. In another there was no appreciable thickening of the arteries.

Summary.—(*a*) There is usually an increase in the amount of connective tissue of the organ.

(*b*) Areas of normal secreting tissue may be present.

(*c*) Glomeruli may be normal in appearance. Some have dilated capsules and some are definitely becoming cystic. They may not be connected with any uriniferous tubule or may be connected with a normal tubule, or with a tubule which is itself becoming cystic.

(*d*) There is usually an increase of fibrous tissue arranged concentrically around the cysts and the glomeruli and tubules which are becoming cystic.

(*e*) The arteries may be normal, or hypertrophied and degenerating.

(*f*) Small cysts may contain a degenerating glomerular tuft or this may have disappeared. They are usually lined with an epithelium which may be cubical or flattened.

It appears, therefore, that the cysts may be derived either from Bowman's capsule or from the first convoluted tubule. This may possibly account for the differences in the appearance of the epithelium in the smaller cysts. The flattened epithelium resembled that lining the glomerular capsule, and the cubical type that of the tubules. The flatness of the epithelium of the large cysts may be due to the continued pressure of their contents.

Microscopical Appearances of the Liver

Rolleston,[8] describing the microscopic appearances of cystic livers in new-born infants, states that there are a number of tubules in the portal spaces which are lined with subcolumnar epithelium, and are somewhat dilated. These closely resemble dilated bile ducts, but are far more prominent, and appear to be more numerous than the normal bile ducts. They may appear completely to encircle the interlobular vein. From the portal spaces these dilated tubes can be traced into the interlobular tissue, and they are accompanied by fairly well-marked fibrous tissue. These epithelial extensions between the lobules are at first somewhat dilated, but as they get further away from the portal space they tend to become solid cylinders, and when cut obliquely may appear to have more than one layer of cells lining them. There are never any masses of bile in these tubes or cysts. The fibrosis thus tends to be interlobular with exaggerations round the large portal canals. There is no intercellular cirrhosis. In the adult form the cysts are much

larger and are surrounded by well-formed fibrous tissue, while there may be numerous blood vessels in the immediate neighbourhood. In the smaller cysts the epithelium is columnar, in the medium-sized ones it becomes cubical or polyhedral, and in the larger ones it is either absent or represented by a few flattened cells. In exceptional cases ciliated epithelium has been described in these cysts.[2] The hepatic cells are, generally speaking, healthy.

Blackburn [7] describes a great increase in the connective tissue in the livers of adults which is especially marked in the portal spaces. In his case there was an excess of richly cellular connective tissue round the bile ducts, many of which were normal, but others showed various stages of dilatation, till they appeared as cysts with well-defined fibrous walls fading away into the surrounding connective tissue. In the larger cysts no definite epithelium could be found, but in the smaller ones it was usually evident and was either flat, cubical or columnar, the nuclei staining well. The liver cells were healthy in appearance and there was an increase of fibrous tissue round the vessels. In connection with this case it must be noted that gall-stones were found in the gall-bladder.

Raymond Johnson [21] states that most of the liver cells are normal and that there is no intercellular fibrosis. The cysts in his case were chiefly in the portal canals and were surrounded by dense fibrous tissue. The linings of the cyst were identical with those described above. Still [5] found in an infant of seven weeks that there was a great excess of fibrous tissue, mostly in the portal area. There was no intercellular fibrosis. The cystic cavities were branched and were not limited to the portal area.

Summary.—(*a*) There is little difference between the infant and adult types, except that the cysts are usually larger in the latter.

(*b*) There is an increase in the connective tissue in the organ which is most marked in the portal area, although in the case recorded in this paper this fact was not definitely demonstrated.

(*c*) The cysts have evidently the same origin as the bile ducts, but, seeing that they contain no biliary material, there is no evidence that they have ever functioned as such. They are lined with flattened, cubical or columnar epithelium depending upon their size.

(*d*) The liver cells themselves are normal.

(*e*) The vessels of the liver are normal.

Pathogenesis

In dealing with the pathogenesis of this condition we are faced with the same difficulty which arose in referring to the literature, namely, that theories are offered to explain the existence of cysts in the kidneys and likewise cysts in the liver, but that often there is little endeavour to correlate the two, and when cysts in other organs, *e.g.* the pancreas, are included there appears to be no further effort to elucidate the problem than to suggest that they are a coincidence.

Any theory, therefore, which is to explain this condition must give satisfaction on the following points:

1. The histological appearances.
2. The fact that several organs may be involved in polycystic disease.
3. The curious phenomenon that the disease appears almost invariably at two periods of life, that is, in the fœtus or young infant and the adult over the age of 40.
4. The hereditary and familial nature of the condition.
5. The frequent coexistence of other congenital abnormalities.

The various theories which have been put forward to explain this condition may roughly be classified under the following headings:

(1) Degeneration.
(2) Neoplasm.
(3) Inflammation.
(4) Errors of development.

I. *Theories of degeneration.*—These suggestions refer mainly to the cysts as they occur in the liver. Pye-Smith [22] thought that they commenced as vacuolisation of the liver cells, but considered the occurrence of cysts in the liver and kidneys at the same time as coincident.

This theory assumes that local destruction of the tissues takes place, and that the cysts form as the result of degenerative changes in the affected areas.

No further evidence has been found to support this theory, and it offers no real explanation of the pathogenesis of the disease.

II. *Neoplastic theories.*—A considerable number of writers have advocated the theory that the condition is of the nature of a new growth, the starting-point in the case of the kidney being the epithelium of the tubules.

Rindfleisch [23] thought that the cysts in the liver were due

to cystic sarcomata starting in the bile ducts. Other writers have considered the neoplasm to be of an adenomatous nature. Malassez [24] and Claude [25] thought that they were cystic fibro-adenomata, analogous to cystic adenomata of the ovaries. Rokitansky [26] suggests that the cysts spring from colloid metamorphosis of the cells. Sabourin [27] considered that the cysts in the liver were "cavernous biliary angeiomata" due to irritation which leads to development of new bile ducts from various sources. Still [5] says of this: "Cavernous biliary angeioma seems an excellent descriptive term, but Sabourin considered that this extraordinary angeioma was a complication of chronic nephritis in adult life, and began as a fibro-epithelial outgrowth in the biliary passages. In these fibro-epithelial nodules numerous alveoli developed, and so the appearance of an angeioma was produced. But apart from the fact that no such complication is known to occur in the liver in cases of interstitial nephritis without cystic kidney, this view does not explain the spaces under the capsule nor the presence of normal bile ducts in the portal area, besides which it is difficult to imagine the occurrence of an intrauterine nephritis which within seven months is complicated by a neoplastic development of duct-like spaces lined with perfect epithelium throughout the liver."

The microscopical appearances of sections of the affected organs may to some extent fit in with these theories, but neoplasms of the types suggested do not have the characteristic of appearing in several organs at the same time, nor have they the same hereditary factor or association with other congenital abnormalities in their nature. Further, there is no evidence of malignancy in this disease.

III. *Theories of inflammation.*—Virchow [28] considered that cystic kidneys were due to a fœtal nephritis leading to a hyper-activity of the interstitial tissue which surrounds, compresses, narrows and finally obliterates the papillæ, which may eventually disappear. Behind the barrier thus formed the products of secretion of the tubules accumulates and leads to dilatation and the formation of cysts. That is to say, he considered the cysts to be retention cysts due to inflammation.

In the same way cysts in the liver have been explained as being due to a primary inflammation of the fibrous tissue round the bile ducts which leads to a dilatation of the latter. In other words, that there is a pericholangitis leading to biliary cirrhosis and later dilatation of the bile ducts, which eventually become cystic.

Still [5] raises the following objections to this theory:

(i) The cysts are far too numerous and may occur just under the capsule at parts of the liver where there are normally no spaces lined with cubical epithelium.

(ii) There has never been a case recorded in which there has been any jaundice, a fact which must throw grave doubt on any obstructive theory.

(iii) Injection of coloured fluid into the ducts does not reach the cysts, *i.e.* there is no connection with the bile ducts.

(iv) The general appearance is not like one of biliary cirrhosis.

(v) On careful examination a perfectly normal bile duct can be found in each portal area.

Blackburn [7] considers that the condition is due to inflammation, and that the irritative factor is a toxic one. He greatly stresses the fact that there is an excess of fibrous tissue round the cysts. A toxic factor would do very well as an explanation, particularly as the organs affected with this disease have an excretory function, but the excess of fibrous tissue can be explained equally well as occurring as a result of the pressure and mechanical irritation of the enlarging cysts, particularly as there is no marked cellular reaction. Again, in no way does it explain the hereditary nature of the disease or the association of other congenital abnormalities with such frequency that they cannot be overlooked.

Still suggests that the excess of connective tissue may be due to the persistence of fœtal mesoblastic stroma, and therefore in itself a congenital abnormality. Another point against the inflammatory theory is the absence of any marked leucocytic infiltration in the neighbourhood of the cysts, especially in the smaller ones which appear to be in the early stages of their development.

IV. *Theories of developmental error.*—The fact that cystic disease of the kidneys is so often combined with cystic disease of the liver, and that both are frequently combined with other congenital abnormalities; that there is strong evidence that it is a familial and hereditary disease, and that it may occur in the fœtus and new-born as well as in the adult, point strongly to this condition being due to an error of development.

Shattock [4] suggested that cysts in the kidney resulted from the want of differentiation of the metanephric blastema from the mesonephos or Wolffian body, and that the remnants of the latter became the seat of the cysts scattered throughout the proper renal tissue. Against this view is the fact that normal

glomeruli of the metanephric type are seen to be becoming cystic and to be directly connected with either normal or cystic tubules.

It will be remembered that the normal kidney develops in two parts. First, there is a tubular outgrowth from the dorsal surface of the Wolffian duct close to its entrance into the cloaca —the ureteric bud—which gives origin to the ureter, renal pelvis and several generations of collecting tubules. The second, is the metanephric blastema, which is derived from the terminal end of the Wolffian ridge, and forms a cap to the ureteric bud, and eventually gives rise to the glomerulus and secreting tubules. These two parts normally unite and a continuous tubular system is established. It has been suggested that failure of union of these two portions leads to dilatation of the nephric tubules derived from the metanephric blastema, and so to cystic formation.

However, cystic formation may be due to the fact that the cells which give rise to the secreting tubules have remained as a solid cord or failed to canalise in one part, so that a retention cyst has resulted, although the two kidney elements have actually united.

In the case of the liver, the bile ducts are apparently derived from hypoblastic cells differentiated from the duodenal diverticulum, and the secreting tissue of the pancreas has a similar origin. It is not difficult to understand how a slight irregularity in development in which some of the columns of cells failed to canalise completely would become dilated spaces lined by epithelium of a similar type as that constituting normal portions of the organ.

It seems, therefore, that there must be some congenital abnormality in the epithelium of the secretory or excretory organs of the body. Associated with this is the fact that a variety of other congenital abnormalities may occur, and that the condition is undoubtedly hereditary. To explain all this one must therefore postulate some definite defect in the germ-plasm of the individual and of his ancestors which may be transmitted to his successors. Whether this defect may arise *de novo* in any individual we do not know.

Why the condition should occur particularly at two periods of life it is difficult to say, but the fact that the arteries are beginning to undergo senile changes in the fifth decade may be an explanation of the onset of symptoms at that age.

In conclusion we may say that in the past the congenital and hereditary nature of the disease has not been sufficiently stressed when its pathogenesis has been considered.

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APNŒA, DYSPNŒA AND CYANOSIS IN RELATION TO ANÆSTHESIA

By M. S. PEMBREY and F. E. SHIPWAY.

PART I. PHYSIOLOGY

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ANÆSTHESIA is a pathological condition, but, as in other pathological conditions, the process has its representation in physiology; it is impossible to discover any change which is unique. It is the same life and the same death which the pathologist and the physiologist observe; the difference is found in the conditions of the subject and the mental attitudes of the observers. For these reasons a mutual benefit results when anæsthetists and physiologists compare their findings. In this paper it is proposed to restrict the comparison to the subject of respiration.

In the first place Apnœa will be considered. The modern significance of the term is an absence of the respiratory movements whereby the lungs are ventilated. In the fœtus a long and profound apnœa is the normal condition for some months before birth; all the so-called mechanisms for pulmonary ventilation are present, but in reserve. If the fœtus be born two or three months before full term, the co-ordinated rhythmic processes of inspiration and expiration can be established efficiently. The fact is beyond dispute, but not the explanation. It is difficult to understand how such a complex series of movements can suddenly arise in response to the need of air to breathe. In muscular work the general rule is progressive training, trial and error, but here in the first breath might appear an exception. This difficulty has been removed by Ahlfeld,[1] whose observations have been confirmed by others. He recorded rhythmic muscular contractions of the human fœtus within the uterus; these shallow movements appeared to be respiratory in nature and to arise from stimulation of the medulla by gaseous changes in the blood. The objection that amniotic fluid would be drawn into the lungs is of little import, for it would only pass in and out of the naso-pharynx and is sterile and isotonic. It is possible also that reflex inhibition may occur if the fluid penetrates too far. Moreover, it is known that the fœtus swallows amniotic fluid.

Cohnstein and Zuntz [2] removed a fœtal sheep from the uterus without damage to the circulation through the placenta; they found that stimulation of the skin, even blowing air into the nostrils, did not cause respiratory movements, but evoked only general reflexes. The premature lamb sucked the experimenter's finger when it was placed in its mouth, and from time to time spontaneously moved its body, but did not draw a single breath until the umbilical cord was tied.

Undue importance has been ascribed to cutaneous stimulation as a cause of the first breath. An infant born in the tropics draws its first breath as readily as one born in a temperate climate or in the Arctic regions. Ahlfeld has shown that infants delivered into a bath at the temperature of the mother's body do not delay their first breath. Breathing by the lungs may commence when the head is in the genital canal: in cases of very protracted labour the full-term fœtus has given respiratory movements inside the uterus, for after death amniotic fluid, fœtal hair and meconium have been found in the trachea and bronchi. On the other hand, it is well known that, if the placental circulation be intact, the fœtus may be subjected to much manipulation in cases of complicated labour or false presentation without being stimulated to breathe prematurely within the uterus.

Cutaneous stimulation can be regarded only as exerting an accessory influence upon the respiratory centre. The effective stimuli are found in changes in the composition of the blood, an increase in the tension of carbonic acid, a decrease in that of oxygen. The equilibrium between acid and base in the blood is maintained by constant adjustments; the respiratory movements are an expression of one of these processes, the removal of carbonic acid.

The excitability of the respiratory centre is low in the fœtus and the infant, for they show a greater resistance to lack of oxygen and accumulation of carbon dioxide than does the adult. A cat will not survive submersion in water for three minutes, but a kitten two days old will recover after it has been under water for as long as twenty minutes. The young mammal retains characteristics of its cold-blooded ancestors. These old experiments [3] have a practical importance in their application to cases of suspended animation in infants at birth.

There is further evidence that apnœa signifies diminished excitability of the nervous system and the absence of sufficient carbonic or other acid to stimulate the respiratory centre; at the same time the evidence shows that apnœa is not due to an

excess of oxygen. In hibernating mammals,[4] such as the dormouse, hedgehog, bat and marmot, the respiratory movements are different in type according to the activity and temperature of the animal. In the torpid animals with a temperature below 12° C. there are long periods of apnœa lasting several minutes and broken only by a few respirations; in the inactive animal with a temperature rising above 13° the periods of apnœa become shorter and the periodicity that of Biot's type [5] with a sudden commencement and cessation of breathing, or the Cheyne-Stokes type with a gradual waxing and waning. During these stages of hibernation the excitability of the animal is profoundly depressed, but there is no relaxation of muscular tone; on the contrary, a rigidity which in some respects resembles that observed in some men during the unconsciousness produced by lack of oxygen.

During sleep Cheyne-Stokes breathing is observed in healthy infants and should be regarded as a physiological condition. The same type of breathing has often been noted in old people during sleep, and here again its significance may have no relation to disease, but to a diminished excitability of the nervous system.

It is well known that morphia will produce periodic breathing, often Cheyne-Stokes in type, and in this connection it is interesting to recall the old treatment, making the patient walk about whether he will or not. The success of this treatment can now be explained as due to the production of carbonic acid in sufficient quantity to stimulate the depressed respiratory centre. Yandell Henderson [6] in recent times has shown the value of the administration of oxygen containing 5 per cent. of carbon dioxide to patients poisoned with morphia. In some places it appears to be the routine practice to give patients an injection of morphia some time before the induction of anæsthesia; the drug depresses the excitability of the respiratory centre, and in patients who are especially sensitive to the drug it may give rise to serious failure of respiration.

The injection of adrenalin into anæsthetised animals will sometimes produce Cheyne-Stokes respiration. This condition, according to the investigations of Ff. Roberts,[7] is due to want of oxygen produced in the respiratory centre by vaso-constriction.

The classical type of periodic breathing called after the names of Cheyne and Stokes is observed in some forms of heart disease and arterio-sclerosis. The periods of apnœa alternating with periods of waxing and waning respiration can be abolished most readily by air containing 3 or 4 per cent. of carbon dioxide, more slowly by high percentages of oxygen such as 80 or 90, or even by a deficient supply of oxygen, such as 12 per cent.

Analyses [8] of the alveolar air of the lungs show in typical cases a low tension of oxygen and a high tension of carbon dioxide at the beginning of the period of breathing, and the opposite during the last waning breaths. Such results indicate that this periodic breathing is due to a diminished excitability of the nervous system associated with a defective supply of arterial blood; the carbonic acid accumulates and the oxygen diminishes until the nerve cells are stimulated, the waxing respirations begin and culminate in hyperpnœa or dyspnœa, whereby a large quantity of carbonic acid is washed out and sufficient oxygen is taken into the blood; apnœa follows owing to the absence of an adequate tension of carbonic acid to stimulate the respiratory centre. The inhalation of air containing more than 2 per cent. of carbon dioxide abolishes apnœa by maintaining the tension of that gas in the alveolar air and the blood at its stimulating value. The administration of pure oxygen by means of a mask and valves abolishes apnœa by maintaining the partial pressure of carbonic acid in the blood at its stimulating level; the respiratory centre is no longer excited by lack of oxygen to send out the forcible impulses which had previously resulted in excessive ventilation, whereby carbon dioxide was washed out of the alveoli and the blood. Air containing a smaller percentage of oxygen than that present in atmospheric air abolishes apnœa; the constant deficiency of oxygen stimulates the respiratory centre.

The same type of breathing has been observed in healthy men after ascents to high altitudes, especially when their excitability was reduced by sleep. Experimentally, as Haldane and Douglas [9] have shown, it is possible to induce this periodic breathing in healthy men by a lack of oxygen due to re-breathing expired air deprived of carbon dioxide by soda lime.

In hysterical patients Cheyne-Stokes respiration has been observed; it can be abolished by suggestion.

There remains for consideration another type of apnœa which was described by Noël Paton [10] and F. M. Huxley as the postural apnœa of diving birds. When a duck is held with outstretched neck in the posture for diving, all respiratory movements are inhibited and a long period of apnœa is the result. The afferent impulses in this reflex arise in the muscles of the neck and in the labyrinths, for the apnœa cannot be produced if the corresponding nerves be divided.

A reflex inhibition of respiration, it would seem, is the chief factor leading to anoxæmia and death in cases of drowning in a few inches of water. The immersion of the face in a depth of water sufficient to cover the nose and mouth appears to

start the sequence of events, whether the act be voluntary as in a case of suicide, or involuntary in epileptics or accidents to healthy subjects.

The apnœa which can be obtained by forced breathing enables a man to remain under water a long time after a dive; this, however, is a dangerous proceeding and has been attended by fatal results in some cases, the diminished excitability produced by the removal of too much carbonic acid causing anoxæmia, unconsciousness and death.

Forced breathing washes out carbon dioxide and produces the condition of acapnia, to which Yandell Henderson [11] has especially directed the attention of anæsthetists.

As long ago as 1876, Addinell Hewson [12] of Philadelphia published in the *Transactions of the International Medical Congress* a paper on the analgesic effects of rapid breathing; he gave an account of his experiments and the operations which he had performed upon his patients during this condition. He found that breathing at a rate of forty or fifty per minute for three to five minutes was necessary for the production of the desired degree of analgesia. The condition was recognised as one of cyanosis by the colour of the patients' lips and cheeks and the blood which escaped during operations. Muscular rigidity was in some cases very definite, in others very slight and transient. The induction of this state he considered to be due to " a diminution in the respiratory function, a cutting off of the normal supply of oxygen and retaining the carbonic acid in the blood to be sent to the nerve centres."

The occurrence, causation and significance of apnœa in health and disease have been considered in detail, because the condition is one of fundamental importance in relation to anæsthesia. The respiratory movements are not only an indication of the ventilation of the lungs, but also of the excitability of the nervous system and the circulation and composition of the blood; they afford more varied information to the anæsthetist than an examination of the pulse.

The counterpart of apnœa is found in the difficult and laboured respiratory movements which constitute dyspnœa. The former, as we have seen, indicates the absence of stimulation; the latter is evidence of vigorous excitation of the nervous system. Similar factors are concerned, for the effects of oxygen and carbonic acid are relative to their tensions and the excitability of the nervous system.

During running an athlete passes through a stage of hyperpnœa followed by dyspnœa, but if in spite of distress he continues to run at the same speed, an adjustment of the output

of carbon dioxide and the intake of oxygen occurs and he obtains what he calls his " second wind." [13] In many contests the condition of the runners at the end is one of anoxæmia.

Cyanosis is a state of anoxæmia, and in its most typical form is seen in mammals immediately after birth. In such cases it is a physiological condition. The disturbance or interruption in the placental circulation has caused a fall in the oxygen and a rise in the carbonic acid of the fœtal blood, two factors which will stimulate the respiratory centre and start the ventilation of the lungs. This form of cyanosis is well known to gynæcologists under the term " blue asphyxia," in contradistinction to " white asphyxia," a condition of anoxæmia accompanied by a failing circulation of the blood.

Sufficient examples have been given to support the contention that pathological processes are not unique but have their representation in physiology. It is now necessary to consider the evidence from the side of anæsthesia. This is given by Dr. Shipway in Part II.

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PART II. ANÆSTHESIA

By FRANCIS E. SHIPWAY, M.D., Anæsthetist to Guy's Hospital.

A FREQUENT cause of apnœa during anæsthesia is the instruction given to the patient to " breathe deeply." Deep breathing washes out too much carbon dioxide. Respiration should be natural, that is, quiet and easy, and any attempt of the patient to breathe rapidly and deeply in order to obtain

unconsciousness in the shortest possible time should be restrained, for it disturbs the natural ventilation of the lungs and the administration. Sometimes this desire arises from nervousness, a feeling of asphyxia, or the memory of a former induction during which this symptom was present. A rapid induction cannot be obtained without a sense of discomfort, for it is impossible to establish rapidly the required tension of the anæsthetic in the blood without cutting down the supply of oxygen and, in the case of chloroform, running the risk of over-dosage.

Apnœa during induction with chloroform may lead to syncope from direct action on the heart, if at the time that breathing is resumed a high concentration of vapour is present and the inspirations are deep. Apnœa may also occur during chloroform anæsthesia, especially in feeble subjects, elderly people, and those who suffer from arterio-sclerosis, if the drug be given by the open method. Cheyne-Stokes breathing may be established. It is caused chiefly by the lowering of the arterial pressure induced by the depressant action of the drug on the heart. The respiratory centre is also depressed and the rate of flow of the blood stream is lessened. Further, Buckmaster and Gardner [1] have shown that even during light chloroform anæsthesia the oxygen capacity of the blood is reduced by 40 per cent. This action of chloroform is serious, for it increases the tendency to anoxæmia. From all these causes the tissues are starved of oxygen, but, on the other hand, it must be remembered that anæsthesia in itself reduces the metabolism and therefore the tissues do not call for so much oxygen. Oxygen should not in consequence be used as a routine. If Cheyne-Stokes breathing should arise, it can be abolished by giving oxygen or carbon dioxide; the latter can be obtained by substituting a semi-open for the open method. On physiological and anæsthetic grounds the semi-open method makes its appeal.

Apnœa is not often seen when chloroform is given through a tracheotomy tube, a condition in which the dead space is much diminished. The explanation appears to be that, although chloroform depresses respiration and produces anoxæmia, the intake of air is unimpeded and the supply of oxygen is adequate in relation to the rise in carbonic acid. Apnœa as a complication is most likely to arise during the anæsthesia produced by intratracheal insufflation, if the ventilation is excessive and carbonic acid is washed out of the lungs and blood. In a case recorded by Pembrey [2] an average ventilation of 16 litres of air per minute was sufficient to oxygenate the blood, but 30 litres per minute produced apnœa for a period of two minutes; the pulse was very good and the blood pressure was 155 mm. at the

beginning of this rapid ventilation. After a minute it had fallen to 138 mm. During the period of apnœa the pressure gradually rose again to 150 mm. As the tension of carbon dioxide in the blood increased, the patient commenced slow voluntary breathing. A sample of alveolar air taken when respiration recommenced showed a percentage of carbon dioxide of 6·04, which is about normal. Analyses of samples of alveolar air taken during the operation showed that the blood pressure followed the carbon dioxide tension. It is not advisable to abolish the respiratory movements during intratracheal insufflation anæsthesia, for their presence favours the exchange of gases in the lungs and maintains the action of the respiratory pump upon the circulation of the blood.

During prolonged anæsthesia with gas and oxygen, in which the expired air is allowed to escape through valves, acapnia may occur. This can be abolished by instituting re-breathing, the amount being regulated to suit each case. An excessive pressure of carbon dioxide leads to sweating, flushing, hurried breathing and a falling pulse rate, while the blood pressure rises at first but falls later; a deficient pressure produces pallor, a cold clammy skin, feeble breathing and a quickening pulse rate. This picture is less often seen to-day than in the past, when Hewitt's apparatus, which makes no provision for re-breathing, was used. Acapnia was not uncommon; it produced all the signs of shock, for which indeed it was mistaken. Acapnia leading to apnœa was seldom seen, for lack of oxygen and the formation of lactic acid in the tissues stimulated the respiratory centre. Exactly what part lack of oxygen and excess or deficiency of carbon dioxide play in any given case it is difficult to say; the problem is so complex. Bayliss [3] found that if excess of carbon dioxide was given to cats, anæsthetised by urethane, together with excess of oxygen, the first effect was a rise of blood pressure, but this was soon followed by a fall. On removal of the excess of carbon dioxide the blood pressure rapidly returned to normal. If there was a deficiency of oxygen, even when the carbon dioxide was absorbed by caustic soda, the blood pressure did not fall so rapidly, but the fall lasted a very long time and was not recovered from for a long time after a normal supply of oxygen. There was often a permanent failure of the respiratory centre.

The danger of a reduced partial pressure of carbonic acid in the blood is increased during administration of gas and ogygen if at the same time there is a deficiency of oxygen in the inspired air. It is known that as the partial pressure of carbon dioxide is diminished the hæmoglobin holds on more tightly to the oxygen.

Thus a condition may arise in which, although the blood is completely oxygenated, the patient may be suffering from anoxæmia. If the percentage of oxygen in the inspired air falls during the acapnia to about 12, the respiration, which has been shallow, may become deep, for lactic acid formed in anoxæmia acts on the respiratory centre and on the dissociation of oxyhæmoglobin in a similar manner to carbonic acid. When morphine or scopolamine has been given, some depression of the respiratory centre exists (although atropine may have been administered at the same time); re-breathing should be instituted almost from the start and the amount increased during maintenance in order to promote absorption of the anæsthetic. Indeed in the absence of re-breathing the respiratory movements may be too slow and shallow to oxygenate the blood although the percentage of oxygen in the inspired air may be high.

Apnœa seldom, if ever, arises during the administration of ether by the open method, as this method is in reality a semi-open one. Analyses [4] of the air under a mask which was covered with two layers of domette and rested upon a pad placed on the face, ether being given by the open or vapour method, showed that the percentage of carbon dioxide was adequate to stimulate the respiratory centre, but was never excessive. The percentage ranged from 2 to 4.

Hyperpnœa and dyspnœa are quickly produced by an excess of carbon dioxide, which may arise from re-breathing or some obstruction in the airway; in the latter case there is also a lack of oxygen. Obstruction of the airway may exist before anæsthesia. The combined effects of this lack of oxygen and excess of carbon dioxide are so serious that it has been well said that the difficulties and dangers of anæsthesia lie largely above the larynx. No one can study the details of fatalities arising during the administration of an anæsthetic without being struck by the part played in their production by neglect of this truth. Falling-back of the lower jaw, retraction of the tongue, laryngeal spasm, accumulation of secretions in the respiratory tract are serious complications of anæsthesia which throw an undue strain upon the nervous and cardio-vascular systems. Of all these complications the most difficult to overcome is the presence of excessive secretions. A small quantity of mucus which becomes churned up and aerated in the larynx and trachea constitutes a danger, especially if the patient's heart be feeble or dilated.

An excessive secretion in the smaller bronchial tubes is highly dangerous, and its removal presents an almost insuper-

able difficulty; this is clearly demonstrated by the following case, the notes of which have been given to the author with permission to publish.

A boy, aged 11 years, was operated upon for acute appendicitis; he looked very ill. The lungs were healthy. Atropine 1/100 grain was injected half an hour before induction, which was carried out by chloroform and ether; open ether was then used. About a quarter of an hour after anæsthesia was complete, slight twitchings of the left arm and shoulder were noticed; they spread within a minute to the whole of the body, becoming so violent that the surgeon had great difficulty in closing the wound. The colour of the patient never appeared really dusky and oxygen did not appreciably relieve the spasms. Chloroform was then given at the request of the surgeon, who thought that the condition was one of ether clonus. About two drachms were given, but there was no effect. The pharynx was mopped out, an intratracheal catheter was passed and a little mucus was sucked out and oxygen was given through the catheter. The spasms became less frequent and settled down into definite attacks, which came on every two or three minutes. In the intervals the boy was quiet, his respirations were shallow and at first rapid, but later they became very slow. Rigidity and spasms then started afresh, and this condition lasted for about three-quarters of an hour. The pulse failed rapidly, and in spite of stimulants and massage of the heart the boy died. At the post-mortem examination the trachea and bronchi were found to be clear, but many of the smaller bronchioles were blocked by mucus, the secretion of which had been profuse. Most of the substance of the lungs was purple and congested, but one lobe of the right lung remained pink.

In this case the cause of death appears to have been anoxæmia. Hewitt recorded two similar fatal cases under the term "mucus inundation."

It is not generally realised that excitement and struggling during induction are often asphyxial in origin, irregular strengths of vapour giving rise to reflex phenomena, such as swallowing and breath-holding, or directly to a feeling of suffocation if such concentrations are high. It is known that by the administration of ether by the drop-method, in which is used a very dilute vapour which is very gradually increased in strength, a difficult subject can be made to pass into anæsthesia with very little excitement. Clinical experience teaches also that the free use of oxygen during induction, particularly when cyanosis pre-exists, whether due to obstruction or an affection of the lungs, largely eliminates or cuts short the so-called struggling stage.

The most interesting of the signs of lack of oxygen—inter-

esting because its significance is often overlooked—is the onset of rigidity and clonic muscular movements, which may be erroneously regarded as an indication of light anæsthesia. It has long been known that abdominal rigidity may be due to anoxæmia and may be abolished by restoring the air-way and supplying oxygen. It is not so well known that certain clonic movements may occur during the third stage of anæsthesia, at a time, indeed, when the slackness of the eyelids and the jaws and the absence of the corneal reflex indicate that anæsthesia is deep. The most common of these are piano-playing movements of the fingers and hands, coupled sometimes with jerky adductor movements of the arms; at other times irregular movements of the shoulders and arms are observed. These athetotic phenomena are of great importance; they are due to lack of oxygen and are, therefore, more common during anæsthesia with chloroform and its mixtures than with ether. A recognition of their nature is essential; less, not more, anæsthetic is required and complete ventilation of the lungs must be secured. These movements are more likely to occur in men, and in anæmic and feeble subjects, especially if the induction has been rapid.

Anoxæmia is shown clinically by cyanosis. There are two kinds of cyanosis. In the first, the arterial and venous pressures are raised, and there is great engorgement of the veins. The colour of the face and of the mucous membranes is blue. The right side of the heart becomes over-distended with blood, and cardiac failure may occur. The engorgement is always associated with an excess of carbon dioxide. This condition is relieved by securing free ventilation of the lungs. In the second variety of cyanosis the veins are not over-full and the colour is grey or leaden. This is the more serious condition, for the circulation is failing. It is associated with a deficiency of carbonic acid, and the indications are to give oxygen and carbon dioxide. Insufflation of oxygen through an intratracheal catheter is sometimes used to restore respiration. It must be remembered that this manœuvre may increase the danger by blowing out carbon dioxide at a time when the tension of this gas is already low. Mouth-to-mouth insufflation is sometimes practised. It has Biblical as well as clinical and physiological support (II. Kings iv, 32–35). It acts by supplying sufficient oxygen and a high percentage of carbon dioxide, and is a method of restoring respiration in desperate cases of apnœa which deserves to be more widely known.[5] The question whether oxygen shall be given in uncomplicated cases has already been answered in the earlier part of this paper. It is unnecessary; indeed it is possible to give an excessive amount of anæsthetic where the

colour of the patient is good owing to the abundance of the oxygen supply. The colour of the blood is an indication of its content of oxygen, but may be no guide to the activity of the tissues. Further, the use of oxygen in uncomplicated cases may tend to disguise a faulty administration.

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NOTES ON A CONSECUTIVE SERIES OF 1080 GASTRIC ANALYSES BY THE FRACTIONAL METHOD

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THE results of test-meals in 425 consecutive cases were recorded in the *Guy's Hospital Reports* by Dr. J. R. Bell.[1] To this series have been added 655 analyses made on Dr. A. F. Hurst's private patients at New Lodge Clinic, Windsor Forest, during the period April 1922 to December 1924 inclusive.

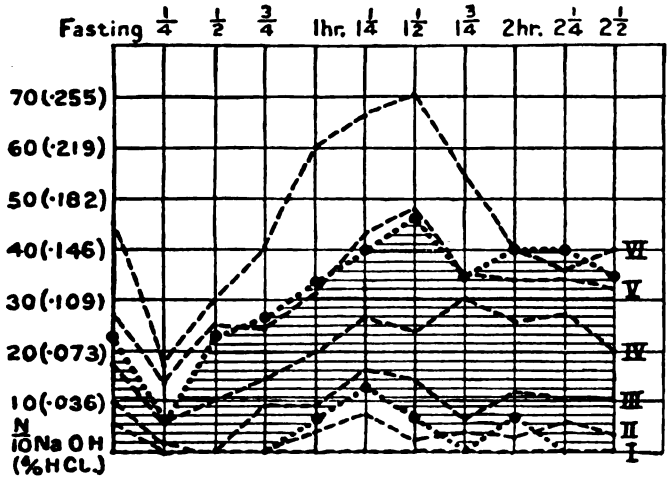

FIG. 1.

The shaded area represents the limits of free HCl (dimethyl indicator) in 80 per cent. of normal people. The dotted lines, I to VI, represent average examples of curves of free HCl in each of the six types of secretion. (After J. R. Bell.)

This makes a total of 1080 consecutive cases admitted for a great variety of medical diseases, many of the patients having no symptoms referable to the stomach. I have extended Dr. Bell's observations to the whole series.

Dr. Bell divided the cases into six groups according to the amount of free hydrochloric acid present, using as a standard for comparison the findings of Bennett and Ryle [2] in a hundred normal students. This classification has been adhered to in the present article. The six groups are as follows (Fig. 1).

I. *Achlorhydria*, in which free hydrochloric acid, as determined by dimethylamidoazobenzene indicator, is present at no period of the analysis. This interpretation of achlorhydria as a true achlorhydria is open to criticism, but, as no other indicator was used in the great majority of the analyses, the term is used here purely as defined above.

II. *Hypochlorhydria*, in which the curve has not exceeded the 10 unit (0·036 per cent. HCl) line.

III. *Low Normal*, in which the curve follows the lower limit of the 80 per cent. normal area.

IV. *Normal*, corresponding to the central zone in which Bennett and Ryle found 59 per cent. of the curves of normal students.

V. *High Normal*, in which the curves approximated to the upper limit of the 80 per cent. normal area, and even exceeded it somewhat.

VI. *Hyperchlorhydria*, in none of which was the free HCl lower than 60 units (0·219 per cent. HCl) at one or more periods of the analysis.

Doubtful cases of hyperchlorhydria have been included with the high normals.

TABLE I.

Age decade.	Achlorhydria.	Hypo-chlorhydria.	Low Normal.	Normal.	High Normal.	Hyper-chlorhydria.
11–20	0	1	5	12	0	0
21–30	11	6	29	60	18	27
31–40	26	22	41	84	32	44
41–50	48	30	41	81	54	48
51–60	44	19	22	80	27	55
61–77	30	8	13	23	12	27
Total . .	159	86	151	340	143	201

The age incidence in 1080 cases classified under the six groups. No children under ten years of age were examined. Eleven cases over the age of seventy years are included in the last decade.

Table I gives the age incidence in decades of the six types of curves of gastric acidity. Fig. 2, based on this table, shows more clearly that, in the hyperchlorhydria group, the largest number of cases occur in the decade 51–60 years, while in the other groups the greatest frequency is seen at an earlier age period.

There were 569 males and 511 females in the series. Their distribution in the six groups is shown in Table II. A separate column shows the number of females after multiplication by the factor 1·113. This has been done in order to reduce the

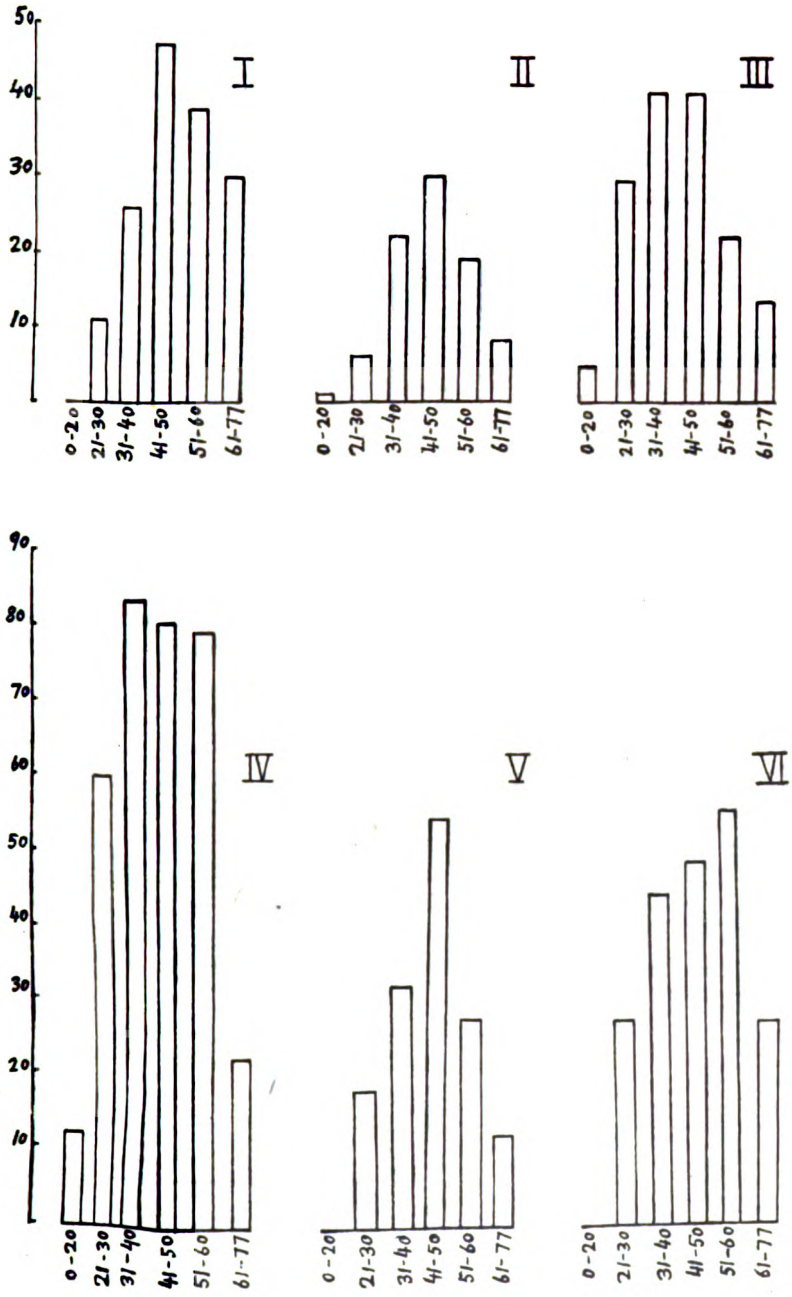

FIG. 2.

A diagrammatic representation of the relative number of cases in the various age decades in the six groups.

figures to a common standard for purposes of comparison. The table also gives the percentage incidence in the sexes, and the average age of each group.

TABLE II.

Type of curve.	Males.			Females.			
	Number.	% of total males.	Average age.	Number.	Number × 1·113.	% of total females.	Average age.
Achlorhydria . .	77	13·5	53·4	82	91·3	16	46·8
Hypochlorhydria .	30	5·3	47·9	56	62·3	11	44·5
Low Normal . .	53	9·3	43·4	98	109·1	19·2	40·6
Normal . . .	167	29·4	44	173	192·6	33·8	39·9
High Normal . .	99	17·4	47	44	49	8·6	38·9
Hyperchlorhydria .	143	25·1	47·3	58	64·6	11·4	44·3

It will be seen that in the higher curves males preponderate over females by 242 to 113·6, and females over males in the lower curves by 262·7 to 160. If achlorhydria is excluded, the preponderance of women over men in the lower curves is even more marked, the ratio being 171·4 to 83.

Fig. 3 shows this difference more clearly. This is a point of practical importance, a moderate degree of hyperchlorhydria in a woman being more noteworthy than the same degree in a man.

The incidence of the various types of curves of gastric acidity in 100 normal students examined by Bennett and Ryle is compared in Table III with the relative frequencies of these curves in the present series of 1080 cases, and in the cases of gastric ulcer, duodenal ulcer and carcinoma of the stomach included in the latter series.

TABLE III.

	Number of cases.	Percentages.					
		Achlorhydria.	Hypochlorhydria.	Low Normal	Normal.	High Normal.	Hyperchlorhydria.
Normal students .	100	4	1	10	59	18	8
1080 consecutive test-meals . . .	1080	14·7	8	14	31·5	13·2	18·6
Gastric Ulcer . .	50	2	8	24	26	20	20
Duodenal Ulcer .	100	0	1	4	16	28	51
Carcinoma of Stomach	23	43·5	21·7	8·7	13·1	8·7	4·3

In the series of 1080 cases the percentage of the normal curve was, as would be expected, much lower than in the healthy students. This difference is mainly due to the greatly increased proportion of extremely low and very high curves in the 1080 patients.

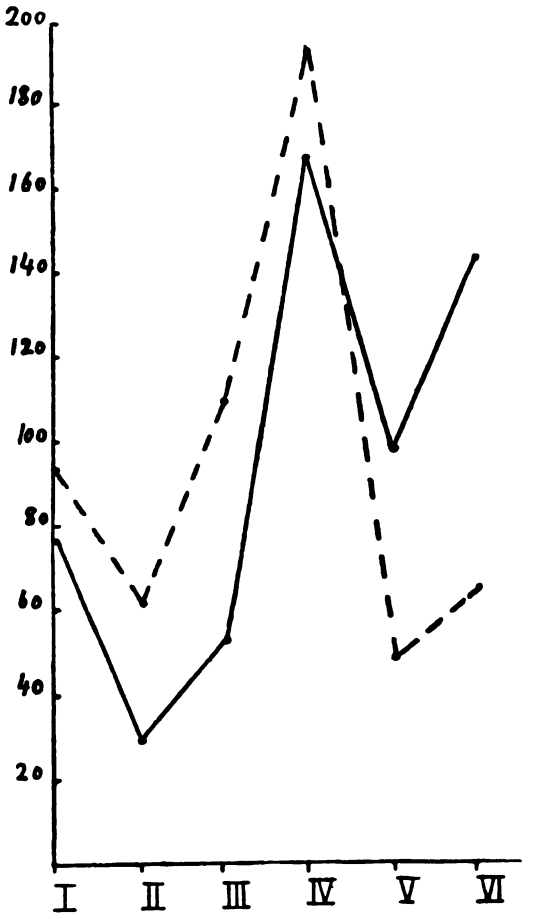

FIG. 3.

Diagram showing the preponderance of women over men in the low curves of gastric acidity (I, II, and III), and of men over women in the high curves (V and VI).

——— males. – – – – – – females.

In gastric ulcer there was a considerable increase in the proportion of low curves and a moderate rise in that of the high curves. Thus, combining the hypochlorhydrias with the low normals, the low curves formed 32 per cent. contrasted with 11 per cent. in the normal series, while the combined figures for high normals and hyperchlorhydrias were 40 and 26

per cent. in the two series respectively. This illustrates the variability of the curves in gastric ulcer from achlorhydria to hyperchlorhydria.

A striking feature of duodenal ulcers was the very large proportion of cases with high curves. Hyperchlorhydria was present in 51 per cent. of the cases, and the high normals and hyperchlorhydrias combined formed 79 per cent. as contrasted with only 26 per cent. in the normal series. There was, moreover, a progressive rise in the percentages from achlorhydria to hyper-

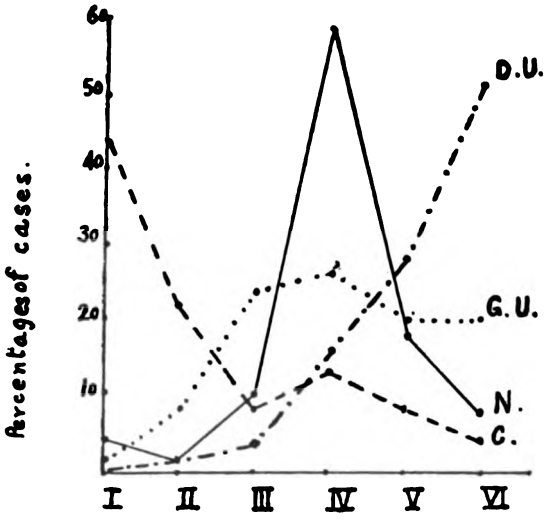

FIG. 4.

Diagram illustrating the relative frequency of the different types of curves of gastric acidity in normal persons, cases of gastric ulcer, duodenal ulcer, and carcinoma of the stomach.

C, carcinoma of the stomach. D.U., duodenal ulcer.
G.U., gastric ulcer. N., normal students.

I, achlorhydria. II, hypochlorhydria. III, low normal.
IV, normal. V, high normal. VI, hyperchlorhydria.

chlorhydria, indicating a definite tendency to high curves in duodenal ulcer.

In carcinoma of the stomach the tendency for the secretion to be reduced was shown by the presence of achlorhydria in 43·5 per cent. of the cases, while the achlorhydrias and hypochlorhydrias together formed as much as 65·2 per cent. High curves were, however, not uncommon, being found in 13 per cent. of the cases.

Fig. 4 illustrates these peculiarities more clearly.

The more common diseases contained in the series are shown in Table IV with the relative incidence of the six types of curves. Both the number of cases and percentages are given. For

purposes of comparison the figures of Bennett and Ryle for normal persons are placed first.

TABLE IV.

Diagnosis.	Number of cases.	Number of Cases.						Percentages.					
		Achlorhydria.	Hypochlorhydria.	Low Normal.	Normal.	High Normal.	Hyperchlorhydria.	Achlorhydria.	Hypochlorhydria.	Low Normal.	Normal.	High Normal.	Hyperchlorhydria.
Normal students .	100	4	1	10	59	18	8	4	1	10	59	18	8
Chronic Gastritis .	30	12	2	5	6	3	2	40	6·7	16·6	20	10	6·7
Gastric Ulcer . .	50	1	4	12	13	10	10	2	8	24	26	20	20
Carcinoma of Stomach	23	10	5	2	3	2	1	43·5	21·7	8·7	13·1	8·7	4·3
Duodenal Ulcer .	100	0	1	4	16	28	51	0	1	4	16	28	51
Gastro-jejunostomy Sequelæ . .	39	7	5	7	9	5	6	17·9	12·8	17·9	23·2	12·8	15·3
Nervous Dyspepsia .	68	3	7	8	25	7	18	4·4	10·3	11·7	36·8	10·3	26·5
Gall-stones and Chronic Cholecystitis .	71	12	3	11	25	12	8	16·9	4·3	15·4	35·2	16·9	11·3
Cirrhosis of Liver .	9	1	0	0	4	1	3	11·1	0	0	44·5	11·1	33·3
Carcinoma of Colon .	10	2	1	2	2	1	2	20	10	20	20	10	20
Chronic Colitis (including Ulcerative Colitis) . .	22	2	2	4	8	5	1	9·1	9·1	18·2	36·4	22·7	4·5
Chronic Appendicitis	41	5	0	6	17	5	8	12·2	0	14·6	41·5	12·2	19·5
Constipation . .	41	2	4	4	21	6	4	4·8	9·8	9·8	51·2	14·6	9·8
Diarrhœa . .	21	5	2	3	7	2	2	23·8	9·5	14·4	33·3	9·5	9·5
Addison's Anæmia (and Subacute Combined Degeneration of the Cord) . .	28	28	0	0	0	0	0	100	0	0	0	0	0
Rheumatoid Arthritis	24	4	5	4	6	2	3	16·7	20·8	16·7	25	8·3	12·5
Neurasthenia . .	126	10	14	25	48	11	18	7·9	11·2	19·8	38·1	8·7	14·3

A few points of special interest in connection with some of these diseases may now be mentioned.

1. *Gastric Ulcer and Duodenal Ulcer.*—In the gastric ulcer cases the sexes were almost evenly represented, there being 27 females and 23 males. The average age was 43·6 years. There was no striking decade incidence, and 56 per cent. of the cases occurred in the fifth and sixth decades.

The sex incidence of duodenal ulcer was 85 males and 15 females, *i.e.* this condition was more than five times as frequent in males as in females. The average age was 49·1 years, and 63 per cent. of the cases occurred in the fifth and sixth decades.

The decade incidence of the two conditions was as follows :—

Decade.	Gastric Ulcer.	Duodenal Ulcer.
1st	0	0
2nd	0	0
3rd	10	6
4th	9	18
5th	16	27
6th	12	36
7th	3	9
8th	0	4
Total . .	50	100

It would appear that duodenal ulcer was relatively uncommon before the age of thirty years.

2. *Carcinoma of the Stomach.*—The nature of the curves in this condition has been described above. Achlorhydria was present in 43·5 per cent. of the cases, and was thus a very much less constant sign than in Addison's anæmia.

3. *Gastro-jejunostomy Sequelæ.*—The patients included in this group complained either of a continuation of the original symptoms after the operation, or of new symptoms. The latter were due to the development of jejunal or gastro-jejunal ulcers, or to stenosis of the stoma, or to entero-colic irritation.

Free hydrochloric acid was absent in 17·9 per cent. of these patients, and curves of high acidity were found in 28·1 per cent.

4. *Chronic Appendicitis.*—Achlorhydria was present in 12·2 per cent., and hyperchlorhydria in 19·5 per cent. compared with 4 and 8 per cent. respectively in normal persons.

It is interesting to compare Bonar's [3] statistics for cases of chronic appendicitis admitted to the surgical wards of Guy's Hospital. In 65 cases he found 33·8 per cent. had achlorhydria or hypochlorhydria, 46·2 per cent. showed curves falling within the normal limits indicated by the shaded area in Fig. 1, and 20 per cent. had hyperchlorhydria. The corresponding figures for the 41 cases in the present series were 12·2, 68·3 and 19·5 per cent. respectively. In normal students Bennett and Ryle found 5 per cent. had low curves (achlorhydria and hypochlorhydria), and 8 per cent. showed hyperchlorhydria. Thus in the present series as well as that of Bonar there is a considerable rise in the percentages of low curves and hyperchlorhydria.

In Bonar's series the rise in the frequency of the low curves is much more pronounced. This may be accounted for by Bonar's finding that achlorhydria was a striking feature in cases of chronic appendicitis, which presented symptoms mainly localised to the right iliac fossa, such cases being, naturally, more frequent in the surgical department. On the other hand, when the symptoms were mainly those of appendicular dyspepsia, hyperchlorhydria was relatively more frequent.

The probable explanation of this is that the absence of free hydrochloric acid in the stomach is a predisposing cause of chronic appendicitis, and that the hyperchlorhydria seen in some cases is part of the reflex appendicular dyspepsia.

5. *Gall-stones and Chronic Cholecystitis.*—Of 71 cases 16·9 per cent. had achlorhydria and 4·3 hypochlorhydria, and 11·3 per cent. had hyperchlorhydria.

In the series of 35 cases of gall-stones reported by Bonar the corresponding figures were 30, 19 and 23 per cent. respectively.

In Table V the cases in Bonar's series are combined with those of the present series, making a total of 106 cases each of chronic appendicitis and gall-stones and chronic cholecystitis. The percentages of the different curves of gastric acidity in normal students are stated for comparison.

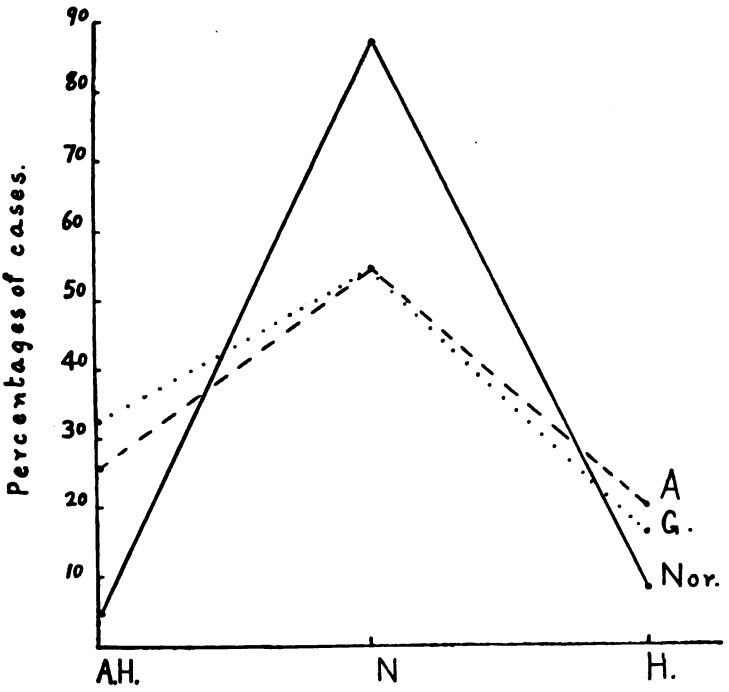

FIG. 5.

Comparison of the relative frequencies of the different types of curves in chronic appendicitis and gall-stones and chronic cholecystitis with those found in normal students.

A.H., achlorhydria and hypochlorhydria.
N., normal limits indicated by the shaded area in Fig. 1.
H., hyperchlorhydria.
A., chronic appendicitis.
G., gall-stones and chronic cholecystitis.
Nor., normal students.

TABLE V.

	Total number.	Percentages.		
		Achlorhydria and Hypochlorhydria.	Normal Limits (shaded area in Fig. 1).	Hyperchlorhydria.
Normal students . . .	100	5	87	8
Chronic Appendicitis . .	106	25·5	54·7	19·8
Gall-stones and Chronic Cholecystitis	106	30·2	54·7	15·1

Fig. 5 illustrates the relatively greater frequencies of low curves and hyperchlorhydria in chronic appendicitis and gall-stones and chronic cholecystitis.

6. *Constipation and Diarrhœa.*—The diarrhœa cases showed a striking increase in the proportion of achlorhydria, free hydrochloric acid being absent in 23·8 per cent. of the curves. The achlorhydrias and hypochlorhydrias combined formed 33·3 per cent. of the cases.

This contrasts with the practically normal frequencies of the different types of curves in constipation (Fig. 6).

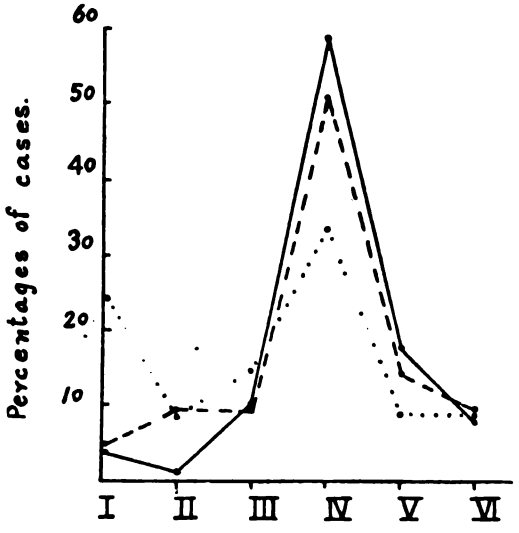

Fig. 6.

Comparison of the relative frequencies of the different types of curves in constipation and diarrhœa with those found in normal students.

——— normal students. – – – – – constipation. . . . . diarrhœa.

I, achlorhydria. II, hypochlorhydria. III, low normal.
IV, normal. V, high normal. VI, hyperchlorhydria.

Achlorhydria is a frequent cause of an irritative form of diarrhœa. In the absence of free hydrochloric acid the disintegration of the food in the stomach is incomplete, and the passage of undisintegrated food into the intestines produces an entero-colic irritation which results in diarrhœa. The causative relationship of the achlorhydria to the diarrhœa is shown clinically by the beneficial effect of the administration of dilute hydrochloric acid with the meals in such cases.

7. *Addison's Anæmia and Subacute Combined Degeneration of the Cord.*—Achlorhydria was invariably present in all the cases.

I wish to thank Dr. A. F. Hurst for kindly allowing me to look through the histories of his cases, and for permission to publish these notes.

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[1] J. R. Bell: *Guy's Hosp. Rep.*, lxxii. 302, 1922.
[2] T. I. Bennett and J. A. Ryle: *Guy's Hosp. Rep.*, lxxi. 317, 1921.
[3] T. G. D. Bonar: *Guy's Hosp. Rep.*, lxxii. 400, 1922.

SOME CASES FROM "CLINICAL"

SERIES III

JANUARY TO MARCH, 1924

Physicians in Clinical:

A. F. HURST, M.D.
G. H. HUNT, M.D.
E. P. POULTON, M.D.
C. P. SYMONDS, M.D.

Clinicals:

M. McC. BAIRD, M.B.
L. J. BARFORD, M.B.
P. C. BENNISON.
J. G. KINGSBURY.
J. D. S. THOMAS.
H. K. WILLIAMS.

TWO CASES OF HÆMOLYTIC, NON-ADDISONIAN ANÆMIA

IT is now well recognised that Addison's (so-called pernicious) anæmia is hæmolytic. Its hæmolytic character can be recognised clinically by the presence of a negative direct with a positive indirect Van den Bergh's reaction. The constant association with past or present oral sepsis and achlorhydria, and the almost invariable discovery of hæmolytic streptococci in the duodenum, suggest that the poison is produced by these organisms, which originate in the mouth and invade the intestine owing to the absence of the normal bactericidal barrier offered by the hydrochloric acid of the gastric juice. It might, therefore, be assumed that a severe case of anæmia, associated with a negative direct and positive indirect Van den Bergh's reaction, septic teeth, and streptococci in the duodenum, must be of the Addisonian type, especially if achlorhydria is present. But it does not appear to be justifiable to diagnose Addison's anæmia in such cases in the absence of megalocytosis and anisocytosis, although the other characteristic features of the blood, such as the presence of megaloblasts and even a high colour-index, may be absent for long periods in the course of the disease. These cases of non-megalocytic, hæmolytic anæmia come under the head of "septic anæmia," which Hunter long ago showed was quite distinct from, though sometimes associated with Addison's anæmia. He claimed that the sore tongue, so frequently present in the latter, is never observed in the former, and in our experience subacute combined degeneration of the cord is only associated with true Addison's anæmia.

The following two cases are reported as striking examples of severe hæmolytic anæmia of a non-Addisonian form. The fatal case clinically simulated infective endocarditis very closely. In the other case oral sepsis was present, and recovery seemed to be due to its removal.

In both cases a diagnosis of Addison's anæmia was rejected primarily because of the blood-picture; the view taken was strengthened by the absence of sore tongue and signs and symptoms of nervous disease, though in the second case complete achlorhydria was present. It is important to note that the mere association of achlorhydria with a severe hæmolytic anæmia does not necessarily prove that it is of the Addisonian variety, though this is in fact nearly always the case; on the other hand, it is doubtful whether true Addison's anæmia ever occurs in the absence of achlorhydria.

Cases of a similar type were published in these "Reports" in April, 1923, (p. 211) and January, 1925 (p. 122); in neither of these was achlorhydria present.

A. F. H.

I

A FATAL CASE OF HÆMOLYTIC, NON-ADDISONIAN ANÆMIA WITH "OSLER'S NODES" SIMULATING INFECTIVE ENDOCARDITIS

By L. J. BARFORD, B.A.

VERONICA C., aged 16, was admitted to Clinical under Dr. Hurst suffering from severe anæmia with pyrexia of 102° F. She was one of a large family and had lived in a South Wales village until the age of fifteen, when she had come to London as a domestic servant. She had never menstruated, and had had no previous illnesses of note; she had always been a pale-complexioned girl.

Her history was that at the age of fifteen, when she started in domestic service, she was able to do her work without undue effort, but for the last few months she had been getting easily fatigued. Three weeks before she was admitted she went to her doctor complaining that the finger-tips of her right hand had suddenly become blue and painful; he found she had a temperature of 101° F. The fingers eventually became numb and painful; red node-like spots appeared on her hands, which also eventually became numb and insensitive; the pyrexia was continuous for the whole of the three weeks before admission, the highest point reached being 103° F.

She had never had a sore tongue and her bowels had been open regularly. She had had a little sickness.

On admission to Clinical she had a temperature of 102° F., a pulse-rate of 120, and a respiration rate of 30. She was very

pale and thin and had the lemon tint so frequently seen in Addison's anæmia.

The fingers of her right hand and to a lesser degree of her left were numb and insensitive to touch; there were several red patches on the hands which were thought to be Osler's nodes. The heart was normal in size and position, the rhythm was of the cantering type, and systolic and presystolic bruits were heard at the apex, but no thrill was felt. Nothing abnormal was found in the lungs. In the mouth there were several carious teeth and some pyorrhœa, but no obvious glossitis. The spleen was enlarged and tender, extending one and a half finger's breadth below the costal margin, and the liver was slightly enlarged.

A trace of albumin but no blood was found in the urine. The urine was sterile.

Examination of the blood showed:

Hæmoglobin 28%.
Red cells 1,880,000 per cub. mm.; Colour-index 0·77.
Leucocytes 30,313 per cub. mm.

Differential count:

Polymorphonuclear cells 62·3% .	18,885 per cub. mm.
Lymphocytes 25·5% . . .	7,729 per cub. mm.
Myelocytes 9%	2,728 per cub. mm.
Eosinophils 2·5% . . .	757 per cub. mm.
Basophils 0·7% . . .	212 per cub. mm.

Seventy-three nucleated red cells and three megaloblasts were seen in a smear, in which 350 white cells were counted.

Poikilocytosis was not marked.

Anisocytosis was well marked.

Clumping took place very quickly in the drawn blood.

The red cells, measured by Professor Adrian Stokes after the method of Dr. Price-Jones (Chart I), showed the average size to be 6·5μ as opposed to the normal of 6·8μ.

Microcytosis was down to 4·5μ (normal 5·2μ).

Megalocytosis was up to 11·6μ (normal 9μ).

Blood culture performed with very careful technique gave a negative result; the same result was obtained a week later.

A Van den Bergh's test performed on the blood serum gave a direct negative and indirect positive reaction. Fouchet's test gave a slow positive reaction.

The patient remained pyrexial and became steadily weaker; the vomiting, which at first had been only occasional, became worse. No free hydrochloric acid was present in the vomit.

Blood counts done at intervals of two or three days showed an increasing anæmia with approximately the same proportion of nucleated reds and megaloblasts as at first, and roughly the same leucocytosis with the same differential count. After a week the hæmoglobin was 24 per cent. and the red cells 1,100,000 per cub. mm.

The heart gradually dilated and the murmurs became more

pronounced. The temperature gradually rose to 105° F. with laboured respiration of 40 to 50 per minute. A few râles were heard at both bases. The patient gradually sank, and died on the thirteenth day after admission.

The post-mortem was performed by Dr. J. A. Ryle and Professor Stokes the next day. All the organs were found to be very pale; there was marked staining of the endocardium and of the large arteries, more especially of the first part of the aorta. The heart-muscle was pale and flabby with marked

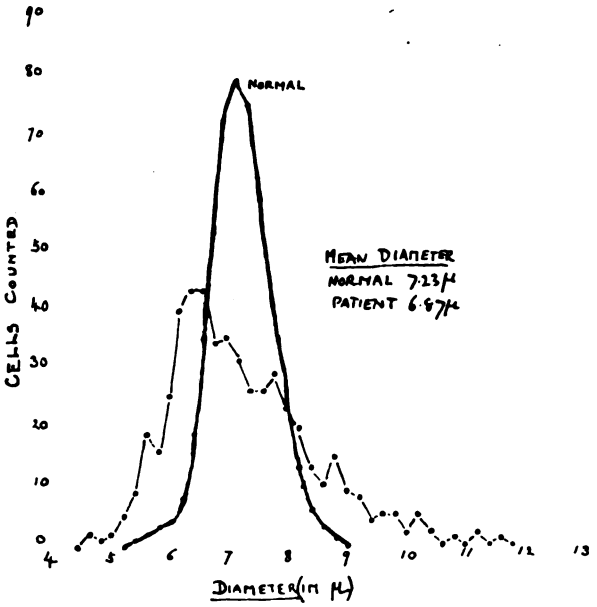

CHART I.

Price-Jones curve of red cell diameters in case of non-Addisonian hæmolytic anæmia.

Patient's curve —·—·—
Normal curve ———

fatty changes in it. One cusp of the mitral valve was œdematous, but there were no vegetations.

The spleen was large and infarcted; it weighed 450 grms.

The liver was large and had a boiled appearance; it gave a slight prussian blue reaction.

The kidneys were swollen and gave a well-marked prussian blue reaction.

The bone marrow was maroon-coloured.

Anaerobes alone were grown from the heart's blood.

Sections of the spleen and kidneys showed numbers of streptococci, but none were present in the infarcts, which suggested that they were due to a terminal infection and had nothing to do with the disease itself.

No streptococci were seen in the sections made from two of the nodes on the fingers.

Commentary

The diagnosis of infective endocarditis, which was made in the first place on account of the cardiac murmurs, Osler's nodes and leucocytosis, but was regarded as doubtful owing to the failure to grow any organism from the blood, was definitely negatived by the post-mortem findings.

The clinical and pathological findings in many respects resembled Addison's anæmia; the marked leucocytosis, however, and the constancy and degree of pyrexia could not be accounted for by this alone. The spleen was not large enough for splenic anæmia in such an advanced stage, and there was leucocytosis instead of the usual leucopenia. The absence of an increase in the average size of the red corpuscles is also important as against true Addison's anæmia.

No other cause for the anæmia was found, and there was no evidence of septicæmia or pyæmia. The indirect but negative direct Van den Bergh's reaction with the positive Fouchet's test showed that some hæmolysis was going on. The streptococci seen in the sections of the post-mortem tissue would have been cultivated from the blood had they been present during life; and had they been the cause of the disease they would have been present in the infarcts in the spleen.

Poynton, Thursfield and Paterson [1] have reported a case of grave anæmia in a child, which is very similar in many respects to this case, and which simulated infective endocarditis almost as completely. Purpuric spots appeared over the legs, bruits were heard in the heart, the spleen was enlarged, and the blood picture was so like that found in this case as to be worth recording here.

Hæmoglobin 25%.

Red cells 1,960,000 per cub. mm.; colour-index 0·6.

Leucocytes 16,400 per cub. mm. (Polymorphonuclear cells 75%; Lymphocytes 24 %; Large mononuclears 1%).

Normoblasts were present.

Blood culture was sterile.

Recovery took place, so there are no post-mortem findings.

Sir Frederick Taylor,[2] under the heading of splenic anæmia, described two cases, a brother and sister, both of whom had had several attacks of anæmia from which recovery had taken place, but eventually each succumbed during an acute attack, the girl at the age of ten, and the boy when he was twelve. Pyrexia was present in both cases. In neither was the spleen very much enlarged and the blood counts were as follows.

The girl :—

Hæmoglobin 16%.
Red cells 1,300,000 per cub. mm.; colour-index 0·61.
Leucocytes 16,000 per cub. mm. (mostly polymorphonuclears).

The boy :—

Red cells 1,000,000 per cub. mm.
Leucocytes 42,000 per cub. mm. (chiefly lymphocytes).

Both gave an iron reaction in the liver, and in both the bone marrow was maroon-coloured. In the girl infarcts were present in the spleen.

A somewhat similar case was in Guy's Hospital a short while ago under the care of Dr. Fawcett. Beatrice B., aged 34, was admitted with thrombosed femoral and subclavian veins; she had a temperature up to 101° F. She had a palpable spleen, red patches in the hands, and a blood count as follows :

Hæmoglobin 35%.
Red cells 1,400,000 per cub. mm.; colour-index 1·2.
Leucocytes 35,000 per cub. mm.

One in ten were nucleated red cells. Blood culture gave no organism.

This case went to autopsy and was found to have many thromboses in the vessels.

It was regarded as a case of Addison's anæmia complicated by some secondary infection the nature of which was unknown.

I think it is justifiable to suggest that all these five cases, if not actually the same disease, have sufficient in common to make them very closely allied to one another. In each there is a severe anæmia of the Addisonian type, except that, with the exception of Dr. Fawcett's case, the colour-index is below unity, there is pyrexia, a moderate leucocytosis, a palpable spleen, an acute termination. Thrombosis in vessels in at least two of the cases had to be distinguished from the embolic processes of infective endocarditis; each, where it is recorded at all, gave negative blood cultures, and in four of the cases death occurred within a few weeks of coming under medical care.

They are scarcely typical of any described variety of anæmia and, with the exception of Dr. Fawcett's case, where the whole condition might have been due to a primary phlebitis giving rise to a septicæmia, no cause was found for the progressing anæmia or for the pyrexia.

In view of the indirect Van den Bergh reaction and excess

of iron in the viscera, and the leucocytosis, nucleated red cells and megaloblasts, it would seem that at any rate our case ought to be regarded as a hæmolytic anæmia caused by some toxic disturbance allied in type but distinct from Addison's anæmia.

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II

CASE OF HÆMOLYTIC, NON-ADDISONIAN ANÆMIA ASSOCIATED WITH ACHLORHYDRIA AND DUE TO DENTAL INFECTION *

By J. F. VENABLES, M.D., Assistant Physician to New Lodge Clinic.

THE patient, a woman aged 59, began to complain of fatigue and loss of appetite in the spring of 1923. Her previous medical history had been uneventful. A number of teeth had been removed during the previous year for pyorrhœa. The symptoms persisted until July of the same year, when improvement took place, which was maintained until the end of September. In October the patient's condition became suddenly worse. Severe vomiting accompanied by great prostration continued for a week. The temperature was raised, reaching a maximum of 103° F. From this attack the patient recovered, but there was a minor relapse a week later, accompanied by diarrhœa and slight pyrexia. She then remained well until January 1924, when diarrhœa reappeared, the stools being pale yellow and extremely offensive; at the same time the temperature rose again, swinging between 98·4° and 100°. The patient's condition was obviously serious. A blood count gave the following figures: red corpuscles 2,500,000 per cub. mm.; hæmoglobin 40 per cent. At one time there had been a moderate leucocytosis present, the figure being 12,600 per cub. mm. Two other leucocyte counts previous to admission showed respectively 4,000 and 7,800 per cub. mm.

The patient was admitted to New Lodge Clinic on January 17, 1924, with a provisional diagnosis of "hæmolytic streptococcal anæmia probably associated with achlorhydria." She was obviously anæmic and very ill. The temperature was swinging between 98·4° and 100°. Physical examination revealed nothing abnormal beyond a soft systolic bruit at the apex which could be traced into the axilla. There were no signs or symptoms to suggest subacute combined degeneration of the cord, and although the patient was very pale, her colour was not the typical lemon-yellow of Addison's anæmia. The spleen was not palpable.

* This is not a "Case from Clinical," but is included for comparison with the foregoing case of anæmia.

The existence of complete achlorhydria was demonstrated by a fractional test-meal. There was no excess of mucus and no blood in any of the specimens, and, as usual in achlorhydria, the stomach emptied very rapidly. The stools contained no altered blood when a farinaceous diet was being taken.

The duodenal contents obtained by means of a Ryle tube gave on culture a strong growth of *B. coli* and *Streptococcus pyogenes longus*. *B. coli* alone was cultivated from the gall-bladder bile. Culture of the contents of the fasting stomach gave the same result as from the duodenal contents, and a similar strain of streptococcus was obtained from the spittle. A fæcal culture consisted of *B. coli* and streptococci, the latter in marked excess, but they were all of the enterococcus type. Blood cultures were made on two occasions when the temperature was raised, but all the tubes remained sterile on incubation.

Of the eight remaining teeth, seven were found to be severely affected with pyorrhœa. Five of them were in such an advanced state that Mr. A. L. Spencer-Payne would have advised extraction even if no symptoms had been present which might be attributed to oral sepsis.

A blood examination carried out on January 21 gave the following results: red corpuscles 2,200,000 per cub. mm.; hæmoglobin 30 per cent.; colour-index 0·7; leucocytes 6,400 per cub. mm. Although there was some variation in the size of the cells, there was no general increase in the mean diameter, and a Price-Jones curve showed that the anæmia was definitely of a non-megalocytic type. Polychromasia and punctate basophilia were observed, but to a very limited extent. No normoblasts or megaloblasts were detected. Van den Bergh's test in the blood serum gave a negative direct and a positive indirect reaction, and the serum itself was abnormally yellow. It was clear, therefore, that the patient was suffering from a hæmolytic anæmia, associated with achlorhydria, which had apparently allowed streptococci from the teeth to invade the intestine, where hæmolytic poisons were produced, the absorption of which caused the anæmia. This is what probably occurs in Addison's anæmia, yet the blood picture was so totally unlike what is found in that condition that a diagnosis of streptococcal hæmolytic (non-Addisonian) anæmia was made. Presumably the specific toxin of Addison's anæmia which leads to megaloblastic activity of the bone-marrow as well as to hæmolysis was not being produced.

By January 28 the patient's condition was obviously worse. There was no marked change in the physical signs except that the spleen became palpable. There had been no diarrhœa since she entered the Clinic. The hæmoglobin had fallen to 25 per cent. Treatment had been started as soon as the investigations were complete. Two drachms of dilute hydrochloric acid were given in ten ounces of water three times a day, the first dose being taken when fasting before breakfast; the second and third doses were taken as a beverage flavoured with orange-juice and sugar at lunch and dinner. In addition the patient took sour

milk three times a day, charcoal, and arsenic. A transfusion was carried out on January 28. Within a few hours the patient complained of mistiness of vision, and on retinal examination multiple hæmorrhages were seen in both retinæ; the discs and fundi had been quite normal on admission. On January 31 the hæmoglobin had risen to 36 per cent., but the general condition was worse; the patient was obviously desperately ill, and the temperature, which had been constantly raised to 100°, was now swinging between 101° and 104°. Her condition did not admit of any vigorous treatment, further transfusion and removal of teeth being considered out of the question while the temperature was above 103°. The hæmoglobin had fallen to 26 per cent. on February 4. The temperature being slightly lower, the patient left the Clinic by ambulance on February 8. Treatment on the above lines was continued at home. Two doses of a vaccine, which had been prepared from a dental swab, were given before discharge, and the vaccination was continued. The slight improvement indicated by the fall of temperature before leaving continued, and it became possible to deal with the oral sepsis.

By March the patient's condition was very different. Treatment had been continued without interruption; all the teeth except one had been removed. Her general condition was good, her appetite excellent. The blood picture had entirely altered: red corpuscles 3,700,000 per cub. mm.; hæmoglobin 70 per cent.; leucocytes 4,500 per cub. mm. On April 30 a further blood count gave the following figures: red corpuscles 4,000,000 per cub. mm.; hæmoglobin 75 per cent.; leucocytes 8,200 per cub. mm. The patient was readmitted to the Clinic on July 9, 1924, for further investigation. She was leading a normal life and appeared well in every respect. The blood picture was normal: red corpuscles 4,460,000 per cub. mm.; hæmoglobin 79 per cent.; leucocytes 6,100 per cub. mm. No abnormal cells were present in a film. Complete achlorhydria was still present, and in consequence of this the patient was advised to continue to take hydrochloric acid indefinitely. Her condition was so satisfactory that no other treatment was deemed necessary.

When seen again in the summer of 1925 the patient looked and felt perfectly well.

APLASTIC ANÆMIA

THE normal quantity of blood present in the body depends upon an accurate balance between the amount destroyed and the amount produced. Anæmia results from excessive blood destruction or deficient blood production, as well as from excessive loss by acute or chronic hæmorrhage. Addison's anæmia is the most familiar though not the only cause of hæmolytic anæmia (*vide* p. 77); chlorosis is probably the best example of deficient production, though its pathogenesis

remains very obscure. Aplastic anæmia is the name given to the rare condition in which the bone-marrow ceases to produce blood corpuscles in sufficient quantity to compensate for their destruction. In very rare cases it appears to be a primary condition. More frequently it is secondary to a primary hæmolytic anæmia, in which the over-activity which is the normal response to both hæmolytic and hæmorrhagic anæmia leads to exhaustion; possibly the toxæmia which is the cause of the excessive hæmolysis also damages the bone-marrow. The first of the two following cases is an example of true primary aplastic anæmia; the second is an example of secondary aplastic anæmia following Addison's anæmia, in which death occurred from anæmia, although the excessive hæmolysis had to a large extent been overcome.

Primary aplastic anæmia is characterised by the absence of nucleated red cells or other evidence of activity of the bone-marrow in response to the anæmia. The anæmia is accompanied by a great diminution in the number of polymorphonuclear and eosinophil leucocytes, showing that all functions of the marrow are impaired, whereas the number of lymphocytes is only slightly reduced; corresponding with this little or no red marrow is found after death. There is no evidence of excessive hæmolysis, van den Bergh's test being negative and no excess of iron being found in the organs after death. Gastric secretion was normal in our case as well as the only two other recorded cases in which a test-meal was given (Roth and Sternberg [1]; R. Schmidt [2]).

Possibly the normal activity of the bone-marrow depends upon the stimulating action of a hormone, which is deficient in primary aplastic anæmia. If this is true, polycythæmia (*vide* p. 90), in which there is excess of red bone-marrow, may be due to excess of this hypothetical hormone, which results in over-activity of the bone-marrow with consequent increase in the number of red corpuscles and polymorphonuclear leucocytes.

A. F. H.

I

CASE OF PRIMARY APLASTIC ANÆMIA

By J. G. KINGSBURY.

JOHN L., aged 22, was admitted under Dr. Fawcett in December 1923, with a history that he was perfectly well until a year before, when he gradually became pale and had occasional attacks of palpitation and giddiness. His appetite remained good, he increased in weight, and continued with his work of motor-driver. During the year he had two attacks of epistaxis, which required plugging.

On his first admission in December 1923, he appeared to be a strongly built man with marked pallor, especially of the mucous membranes, but no yellow tinge. A few purpuric spots were found on the body. The liver and spleen were not palpable, and no evidence of disease was found in his chest, abdomen or nervous system. The blood examination on admission showed:

Red corpuscles 2,600,000 per cub. mm.
Hæmoglobin 27 per cent.; colour-index 0·56.
White corpuscles 3,000 per cub. mm.
Differential count: polymorphonuclear cells 59%.
lymphocytes 38%.
large mononuclears 2%.
eosinophils 1%.

There was slight anisocytosis with a few microcytes, but no other morphological abnormality was found in the red cells. Platelets were rare. The Wassermann reaction was negative. Van den Bergh's reaction was negative.

A fractional test-meal showed a low curve, but on two subsequent occasions slight hyperchlorhydria was found. The x-rays showed no abnormality in the stomach or duodenum. Clinical and radiological examination of the teeth showed no focus of infection.

He was treated with iron, arsenic and hydrochloric acid, and had three blood transfusions. On discharge 2½ months after admission, the hæmoglobin percentage had risen to 44, but the red corpuscles numbered only 2,500,000 per cub. mm., the colour-index being now 0·86. The leucocytes numbered 2,500 per cub. mm., with polymorphonuclear cells 48 per cent., small lymphocytes 43 per cent., large lymphocytes 7·1 per cent., and basophils 1·9 per cent., but no eosinophil cells.

He was readmitted under Dr. Fawcett at the end of April 1924, and was again breathless and found it difficult to carry on with his work. Purpuric spots were again present with small conjunctival hæmorrhages, and a hæmic systolic murmur was heard over the heart. He remained in hospital till August. On discharge after three more transfusions the hæmoglobin percentage was 37, and the red corpuscles numbered 2,125,000 per cub. mm.

He returned to his motor-driving, but was readmitted under Dr. Hurst in November 1924. The blood examination now showed:

Red corpuscles 1,450,000 per cub. mm.
Hæmoglobin 28 per cent.; colour-index 0·97.
White cells 3,600 per cub. mm.
Differential count: polymorphonuclears 39%.
lymphocytes 43%.
hyalines 3%.
myelocytes 13%.

The average size of the red corpuscles was not increased. No nucleated cells were found.

Between this date and that of his death on April 17, 1925, strenuous efforts were made to stimulate his bone-marrow without success. The red cells and hæmoglobin gradually fell, while it was very noticeable that the white cells in the blood rapidly diminished and that blood transfusions and other treatment made no difference to this fall.

Mr. Bromley removed a small piece of bone with some bone-marrow from the upper end of the right tibia on December 15. Only the minutest trace of red marrow was found.

Iron and arsenic were given to the extent of 60 minims of liq. arsenicalis with 60 grains of iron and ammonium citrate daily.

A course of intravenous N.A.B. was tried, and also subcutaneous injections of normal horse serum. Seven more transfusions were given. A small dose of deep x-rays was applied to the knees.

Death in the end was accelerated by a profuse epistaxis, which followed upon a long period of bleeding from the gums.

Post-mortem findings.

Multiple hæmorrhages all over the body beneath the skin, the mucus membranes and serous surfaces. Much subcutaneous fat, and fatty infiltration of abdominal viscera. No visible red marrow—simply fat: humerus, tibia and sternum sawn open. Microscopically fat spaces with no narrow tissue seen. Heart fatty, dilated and hypertrophied.

Prussian blue test strongly positive in liver, faint in spleen and kidneys. On microscopical examination hæmosiderin granules were very numerous in the liver, but none seen in the spleen or kidney.

REFERENCES

[1] N. Roth and F. Sternberg: *Med. Klin.*, xviii. 274, 1922.
[2] R. Schmidt: *Med. Klin.*, xv. 595, 1912.

II

APLASTIC ANÆMIA SECONDARY TO ADDISON'S ANÆMIA

By H. K. WILLIAMS.

J. H., an unmarried woman, 30 years of age, was admitted to Mary Ward under Dr. Hurst in April 1924. Her previous history was uneventful until 1921, three years before admission, when she began to feel easily tired. During this period she became progressively weaker, and suffered from what she described as bilious attacks. In 1923 these attacks became more frequent, and she was admitted to the Glasgow Western Hospital in May 1923, where she was treated for pernicious anæmia.

On admission to the above hospital she was found to have a

hæmoglobin percentage of 40, a red cell count of 1,500,000 per cub. mm. (colour-index 1·3), and a white cell count of 3,000. She was given iron and arsenic by mouth and responded well to treatment, her red cell count rising to 6,500,000, hæmoglobin to 85 per cent., with colour-index 0·6, and white cell count to 9,000, in twelve weeks, when she was discharged to a convalescent home.

The patient remained perfectly well until December 1923, when she again began to experience the same chain of symptoms, with bouts of vomiting lasting for four to five days, associated with epigastric pain, which continued till her admittance in April 1924.

She was found to be very anæmic and to have the characteristic lemon-yellow colour associated with Addison's anæmia. She was edentulous, all her teeth having been extracted eleven years previously. Her tongue showed evidence of glossitis, and she gave a history of occasional attacks of sore tongue during the past few years. Nothing abnormal was found in the respiratory or cardio-vascular systems. The central nervous system showed no evidence of organic disease. The abdomen was supple, but there was definite tenderness in the epigastric and appendicular regions. The spleen could not be palpated and there was no enlargement of the liver. The bowels were loaded and the patient gave a history of constipation for some years.

Blood examination revealed the following information :— group 4; hæmoglobin 48 per cent.; red cells 2,350,000 per cub. mm.; colour-index 1·07; white cells 3·700 per cub. mm. The red cells were typically megalocytic. Van den Bergh's reaction : indirect positive; direct negative. Serum distinctly yellow.

A fractional test-meal showed complete achlorhydria.

Chemical examination of the fæces showed very marked hæmatin and hæmatoporphyrin spectra and a very strong guaiac reaction.

X-ray examination of stomach and duodenum revealed no abnormality (P. J. Briggs).

Bacteriological examination revealed the presence of a hæmolytic (30 per cent.) and a non-hæmolytic (70 per cent.) *Streptococcus longus* and a *Staphylococcus albus* in the spittle, resting juice from the stomach, and the duodenal contents (F. A. Knott).

After a short period of resting in bed the patient lost all epigastric tenderness, but the signs in the right iliac fossa did not disappear. It was decided to remove the appendix, and this was done by Mr. R. P. Rowlands. The same two strains of streptococcus were isolated from material obtained by puncture of the duodenum during the operation. The stomach and duodenum were examined and found normal. Before the operation, her hæmoglobin was 39 per cent., and fourteen days afterwards it was 25 per cent.

Blood transfusion was done, three-quarters of a pint of defibrinated blood being given, and her hæmoglobin rose in

three days to 45 per cent., in marked contrast to the absence of response later in the course of the disease.

During the following months the patient made little real headway, in spite of intensive treatment, including vaccines prepared from the duodenal hæmolytic streptococcus, serum injections, blood transfusions and intravenous arsenic, in addition to large doses of arsenic and iron by mouth, together with hydrochloric acid. Occult blood in quantity was present in the stools throughout the course of the illness, though the explanation of this very unusual symptom of Addison's anæmia was never discovered, even at the post-mortem.

In July and August the hæmoglobin fluctuated between 41 per cent. and 32 per cent., and the red cell count fell from 1,750,000 to 1,500,000, on two occasions being below 1,300,000 per cub. mm. All blood films showed changes typical of Addison's anæmia, but the number of nucleated red cells was never above 3 per cent. in a differential count of 300 leucocytes. The patient still retained the typical colour associated with this type of anæmia.

In September and October the drop in the red cell count continued, being 1,029,000 per cub. mm. at the end of October, whilst the hæmoglobin, varying between 36 per cent. and 23 per cent., had fallen to 24 per cent. Blood transfusion early in November was followed by a transitory rise in the hæmoglobin content, the figure reaching 36 per cent. within five days, but this was not maintained, and at the end of the year the figure was again below 25 per cent. By this time the characteristic colour was not so marked, and the patient looked more waxy than yellow. Nucleated red cells were only occasionally seen in the blood films, and the response to blood transfusions was less marked and not so long sustained.

In January 1925, when the case first came under Clinical, the patient presented a picture more in accord with that of an aplastic anæmia. She was no longer lemon-yellow in colour, except for short periods at a time, when she suffered from what appeared to be blood crises evidenced by pyrexia with vomiting and diarrhœa. Blood films at this stage showed marked anisocytosis and poikilocytosis, but megalocytosis was no longer well marked, and a careful search did not reveal any normoblasts. The colour-index was 1·5. There was a definite leucopenia. A Van den Bergh test at this stage was inconclusive, but later gave a negative direct, and positive indirect reaction.

Owing to the failure of the bone-marrow to respond, it was decided to try the effects of stimulation by exposure to a very small dose of deep x-rays, and with this end in view her tibiæ were treated for twenty minutes, but with little reaction.

During the last month the patient's hæmoglobin was in the neighbourhood of 15 per cent., with a red cell count of about 700,000 per cub. mm. She died in June 1925.

At the post-mortem examination the tissues were all very pale. The organs gave a very strong iron reaction, but the bone-marrow was pale and fatty, wanting in all signs of blood regeneration.

Commentary.

The case is of interest in that it shows the gradual change from a typical Addison's anæmia, with remissions and bone-marrow response—as shown by the presence of normoblasts, and hæmolysis—as shown by the typical lemon-yellow colour and Van den Bergh reaction, to one of aplastic type with continued fall in the red cell count and hæmoglobin content, without bone-marrow response, and with very little hæmolysis. Presumably this was due to the prolonged action of the toxæmia and anæmia on the bone-marrow, so that when the infection and consequent hæmolysis had been to a great extent overcome, recovery was no longer possible owing to the inactivity of the bone-marrow.

A CASE OF SPLENOMEGALIC POLYCYTHÆMIA

By J. G. KINGSBURY.

PETER S., aged 57 years, was admitted under Dr. Hurst on January 19, 1925, with shortness of breath, weakness and enlargement of the abdomen starting one year previously. He had been engaged in sulphate of ammonia manufacture all his life, which had been singularly healthy. Previous illnesses were typhoid fever thirty-four years before, and fourteen years later an attack diagnosed as "gas poisoning" by his doctor, which kept him from work for a fortnight. Both his father and mother lived to be over eighty, and he denied any familial tendency to a markedly ruddy complexion.

Just over a year ago he began to notice enlargement of his abdomen, with shortness of breath on exertion and a feeling of weakness which interfered with his work. He went to his doctor, who sent him to an infirmary for nine weeks, where he was told his spleen was enlarged and was given x-ray treatment (not "deep x-ray therapy") twice a week. This treatment was continued till his arrival at Guy's, during which time he never left the house except to go to the infirmary twice a week. He experienced severe itching at times, which was relieved by bleeding, his own doctor taking off a pint of blood on three occasions.

On admission the patient was seen to have a very red complexion, which rapidly changed to a cyanotic colour on exertion or on lying flat on his back. He was well covered.

The teeth were very septic and the gums retracted. Palpation of the abdomen immediately drew attention to the spleen, which was very large. It filled the left loin, reaching to the iliac crest, whence the sharp anterior border passed upwards and to the right, passing two fingers' breadths below the umbilicus to a point 2½ inches to the right of the mid-line. At this point it turned upwards and to the left, formed two large notches and

disappeared under the costal margin and tip of the xiphisternum. The liver was definitely enlarged, but only slightly. The patient had had no dyspeptic symptoms or trouble with his bowels.

The heart was not enlarged and no bruits were heard. The systolic blood-pressure was 125 mm., and the diastolic 90.

Blood Examination by Professor Adrian Stokes
(January 25, 1925)

Hæmoglobin 115%.
Red cell count 8,320,000 per cub. mm.
White cell count 13,400 per cub. mm.
Colour-index 0·69.
Differential cell count:
Polymorphonuclears 88%.
Small lymphocytes 5%.
Large lymphocytes 2%.
Mast cells 3·3%.
Transitionals 1%.
Eosinophils 0·7%.
Blood urea—normal.
Alkali reserve—normal.
Wassermann reaction—negative.

Van den Bergh's reaction gave a negative direct and slightly positive indirect reaction. The excess of bile pigment in the blood was presumably due to the normal hæmolysis of the excessive number of red cells present.

Exercise Tolerance Test (stool 13 inches high).—He was quite incapable of doing this exercise twelve times to the minute, usually giving up at the end of one minute. His pulse and respirations quickened very little, being respectively under 90 and 30. His excuse for stopping was, "I feel tired right out, as after a ten-mile walk."

Having completed these investigations, it was decided to try the effect of bleeding. One pint of blood was taken off on February 4, 1925, and another pint two days later. The first pint affected him very little and barely lowered the blood count, but the loss of the second pint of blood weakened him considerably and greatly lowered the hæmoglobin and red cell count.

Red cells 6,670,000 per cub. mm.
Hæmoglobin 93%.
Colour-index 0·69.

The systolic blood pressure also fell to 110 mm., and the diastolic to 80 mm.

He soon recovered from the effects of the blood loss. During the following month his blood count and blood pressure remained stationary. It is interesting to note that at the end of the month his exercise tolerance reaction was identical with that on admission, clearly disproving the theory of excessive blood viscosity as the cause of distress in polycythæmia.

It was next decided to treat him with phenylhydrazine hydrochloride. This was given from the 5th to the 24th of March, the dose being gradually raised from 0·1 to 3·3 grammes given in a cachet, with the following results :

	Hæmoglobin per cent.	Red corpuscles per cub. mm.	Colour-index.
23.2.25	90	6,800,000	0·66
4.3.25	90	6,400,000	0·70
Treatment begun : 5.3.25			
7.3.25	88	6,880,000	0·64
9.3.25	86	6,800,000	0·60
15.3.25	86	6,560,000	0·66
23.3.25	78	6,560,000	0·59

The above table shows that this treatment was not successful. The red cell count was little affected, while the hæmogobin rapidly fell, thus giving a fall instead of a rise in the colour-index. The patient himself was also much upset; he experienced attacks of dizziness and was obliged to stay in bed for a time.

As bleeding and the phenylhydrazine treatment had proved ineffective, Dr. Watt was now asked to try the effect of deep x-ray therapy. The patient was rapidly recovering from the effects of the phenylhydrazine. The size of the spleen and the high relative polymorphonuclear count were unchanged all this time.

Deep x-ray treatment was started on April 7th, the application being to the knees for twenty-five minutes. Further treatment was given on May 17th and 22nd, soon after which the patient was discharged. The blood picture was now as follows :

Hæmoglobin 193%.
Red cells 9,000,000 per cub. mm.
Colour-index 0·6.
White cells 13,000 per cub. mm.

Contrary to expectation, the x-rays caused the red cell count and hæmoglobin percentage to rise rapidly; unfortunately it failed to raise the colour-index. The spleen became definitely smaller, the anterior border being one finger above the umbilicus instead of two fingers below, and it was now movable in the abdomen instead of being tightly wedged on account of its great size. Except for this, in spite of four months' vigorous treatment, the patient was in an almost identical condition to that on admission.

The patient was readmitted on September 22, 1925, for further deep x-ray therapy. He said that while at home he had been definitely better than before admission. He had been walking about a mile a day. Clinically his condition

showed little change. The size of the spleen had not altered appreciably. The blood examination now gave the following result :—

Hæmoglobin 108%.
Red cells 8,060,000 per cub. mm.
White cells 20,000 per cub. mm.

Dr. Campbell found that the fragility of the red blood corpuscles was normal. This disposes of the theory that the polycythæmia might be due to an increased resistance of the red blood cells.

The systolic blood pressure was now 117 mm., and the diastolic 84 mm.

Commentary

It has generally been assumed that the dyspnœa of polycythæmia—the chief symptom of which our patient complained—is due in some way to the excessive number of red corpuscles present in the circulation, and many have thought that this is a result of increased viscosity interfering with the proper flow of blood. The obvious treatment for the condition would therefore appear to be to reduce the amount of blood in the circulation. This can be accomplished rapidly by bleeding, slowly by the use of some such drug as phenylhydrazine, which destroys the circulating blood, or, most rationally, by reducing the production of blood by destroying or inhibiting the activity of some of the excess of red bone-marrow in the bones.

Each of the methods of treatment was tried in succession, but no improvement in the dyspnœa resulted, even when the number of corpuscles was considerably reduced. It is clear, therefore, that some other cause of the dyspnœa should be looked for, although improvement has in the past been reported in a few cases treated by each of the three methods mentioned.

Polycythæmia might conceivably be due to a primary overactivity of the bone-marrow, the direct opposite of primary aplastic anæmia (*vide* p. 84). The former might be due to excess and the latter to deficiency of a hormone, the function of which is to regulate the normal blood-producing activity of the red marrow. If this were the case, the symptoms should disappear with a reduction in the quantity of blood, and the most rational treatment would be radiotherapy of the bones in dosage just sufficient to keep the quantity of blood at a normal level. The cases which have been reported in which such treatment has met with success may perhaps have been examples of a primary polycythæmia of this kind.

It is also possible that the polycythæmia is secondary to some abnormal condition leading to dyspnœa, the polycythæmia

being due to an attempt to compensate for this by increasing the amount of hæmoglobin available for combining with oxygen. The condition would then be comparable with the polycythæmia present in residents in high altitudes. In the latter, however, the compensation is adequate and the dyspnœa disappears within a short period of the individual's arrival, and the spleen does not become enlarged. If this were the cause of the polycythæmia in our patient it would, of course, explain why no improvement followed a reduction in the quantity of blood. We were, however, unable to discover any such cause.

A. F. H.

TWO CASES OF RECURRENT GASTRIC HÆMORRHAGE WITHOUT ORGANIC LESION AND ASSOCIATED WITH OTHER HÆMORRHAGES

By L. J. BARFORD, M.B.

I

A CASE OF RECURRENT SEVERE HÆMATEMESIS WITH OCCASIONAL EPISTAXIS AND HÆMATURIA

Frances H., aged 22, was admitted in a critical condition, having had several severe hæmatemeses during the preceding six days. She was still bleeding when admitted.

Her history was that six days before admission she had been seized with a severe attack of abdominal pain for no apparent reason; she had vomited soon afterwards. Later in the day the pain passed off, but in the evening she vomited again, and this time the vomit contained blood. The vomiting continued two or three times a day until she was admitted to hospital. Each vomit contained bright red blood. There had been occasional pain, but it was not constant, nor did it precede each attack of vomiting. Her former history was that she had had three similar attacks during the last four years; each attack had lasted some weeks, and on each occasion she had been operated on for it. The only direct information from the surgeons concerned which we could obtain was of the last operation: here the abdomen had been opened, but owing to the many adhesions, nothing could be done, so the wound had been immediately closed.

On the day of admission she vomited twice, and each time the vomit contained bright red blood; one attack was preceded by abdominal pain of a colicky nature.

Her hæmoglobin was 57 per cent. She was infused by rectum with saline solution and kept quiet with morphia. Physical examination revealed nothing except some tenderness in the epigastrium, more especially over the upper part of the old operation scars; the spleen was not palpable. There was

no rigidity between the attacks of vomiting. It was thought that the condition was an ordinary hæmorrhage from a gastric ulcer. The hæmatemesis, in spite of the morphia, continued, and on the third day after admission the abdomen became very rigid, the temperature, which up till then had been normal, became slightly raised, the pulse-rate remained roughly the same, but the respiration rate increased considerably; it was thought at one time that perforation had occurred, but the pulse remained constant and eventually the rigidity became less and what pain there was disappeared, so that although all preparations had been made for an operation it was never performed.

The vomiting continued for a week despite all efforts to keep the patient quiet with morphia. Each vomit contained a certain amount of bright red blood; the rest of it must have been gastric juice and swallowed saliva, because the patient was not allowed anything by mouth.

Horse serum and calcium chloride were injected, but the bleeding continued. The stomach was washed out and adrenalin poured down the stomach tube, so that a drachm was left in the stomach. This was done on several occasions, and although it appeared to have some immediate effect in stopping the bleeding, it only lasted a few hours. The patient had considerable dental sepsis, and it was decided that this should be eradicated on the assumption that the condition was probably not a chronic ulcer, but that there had been a succession of acute ulcers of dental origin. Several teeth were removed under chloroform anæsthesia during one of the respites from vomiting. On the whole the condition seemed to improve after this; the vomiting became less frequent, and eventually after about a week ceased altogether, only to recommence five days later.

There was no more than the ordinary amount of bleeding after the extractions.

Three weeks from the time of admission there was a fairly severe epistaxis; the nose had to be plugged to stop it; this occurred again a few days later, and the blood was seen to be coming from a mass of granulation tissue on the septum.

Hæmaturia was also noticed on several occasions.

At the end of three weeks the hæmoglobin percentage had fallen to 40.

An x-ray examination after an opaque meal showed that the stomach was small and emptied rapidly; there was no sign of any short-circuiting operation having been performed.

When the condition became complicated by the epistaxis and hæmaturia, it was decided that the diagnosis ought to be revised again, and with a view to this several investigations were carried out. A liver efficiency test was performed with 50 grms. of lævulose; this showed that there was some slight deficiency in liver function.

A urea concentration test showed normal concentration.

The blood platelets were counted and found to be normal—

about 300,000 per cub. mm. The coagulation time was 1 min. 56 sec.

The vomiting continued at intervals, there being sometimes as much as four days of complete freedom.

The taking of fluids by the mouth seemed to have no effect either in stopping the bleeding or in making it worse, but on the whole the feeding was done by rectum.

At the end of eleven weeks the hæmoglobin had fallen to 26 per cent. Shortly afterwards hæmatomata appeared in the subcutaneous tissues, but there was no true purpura. In view of this, and in spite of the normal platelet count, which was confirmed on several occasions, it was decided that the condition must be due to a general hæmorrhagic tendency similar in character to Henoch's purpura. All other methods having failed to stop the bleeding, a course of peptone injections was begun; 0·3 c.c., 0·5 c.c., 0·7 c.c. and 0·9 c.c. of 5 per cent. peptone were injected intravenously at four-day intervals. This marked the low-water level, and from the day of the first injection recovery began. No more vomiting occurred, there was no more hæmaturia or epistaxis, and by the end of the course the patient was sitting up in bed and eating with great enjoyment the moderate diet she was allowed. With careful feeding the hæmoglobin gradually rose so that she was able to be sent to a convalescent home within a month of the first peptone injection. Recovery continued, and within three months of her transfer to the convalescent home, her hæmoglobin percentage had reached 60. She was discharged and is now, nine months afterwards, doing light domestic duties, having had no recurrence of symptoms.

Commentary

The history of the previous attacks, the operation scars, and the fact that the bleeding was apparently only occurring in the stomach made a diagnosis of a bleeding ulcer, either chronic or acute, completely justifiable. It was not until nearly a month later that the epistaxis threw some doubt on this. It was, however, at the time, regarded as accidental, but when the second attack occurred, and with it the hæmaturia, the idea of a simple bleeding ulcer of any kind had to be given up.

The examination of the blood revealed no clue; the differential leucocyte count was normal, the number of platelets was normal, and the coagulation time was less than two minutes with a fairly good retraction of the clot. When the hæmatomata, three months after admission, appeared it seemed fairly clear that the condition was an obscure form of hæmorrhagic disease, somewhat resembling Henoch's purpura.

The remarkable effect following the injection of peptone may have been only a coincidence, but from the fact that the

recovery was so rapid it seems likely that there was some therapeutic action, more especially since the vomiting ceased after the first injection, although during the few previous days the bleeding had seemed to get even more out of control than at any earlier time.

This case is interesting in that it shows that in a condition of the purpura type there can be continued and dangerous hæmorrhages from mucous surfaces without the slightest trace of cutaneous hæmorrhage, the subcutaneous hæmatomata being the nearest approach to it, and these only occurring a long time after the initial onset.

II

A CASE OF RECURRENT MELÆNA FOLLOWING AND ASSOCIATED WITH RECURRENT EPISTAXIS

WILLIAM R., aged 34, was admitted to hospital suffering from melæna. His history was that up to the age of seventeen he had had many attacks of epistaxis, but that since then they had been less frequent. From the age of seventeen he had had attacks of melæna, but never hæmatemesis, which started suddenly and lasted a variable time, from a few days to a month. He had been free for as long as three years at a time, but recently they had occurred at intervals of one to five months; his last attack ended five weeks before onset of this attack for which he was admitted.

During attacks of melæna he suffered from dyspnœa, which got worse the longer the attack lasted, palpitation, and slight indigestion, which had no particular relation to meals; he was never sick nor did he have any severe abdominal pain. Between attacks he was perfectly well.

His father suffered all his life from unaccountable epistaxis, and one of his two brothers had had an attack of hæmaturia, for which no cause could be found.

On admission to hospital the patient looked pale and was evidently suffering from considerable anæmia. Nothing abnormal was found on general examination; there was no purpura and nothing abnormal in the urine; there were no hæmorrhages in either fundus.

The stools were soft, black and sticky; they contained much acid hæmatin, some hæmatoporphyrin, and gave a strongly positive guaiac reaction.

The hæmoglobin was 50 per cent. The red cell count was 3,600,000 per cub. mm, the colour-index being 0·79. The white cell count was 10,000 per cub. mm, the differential count being normal. The platelet count was 216,000 per cub. mm., and the clotting-time was 1 min. 55 sec., both being within normal limits. The blood gave a negative Wassermann reaction.

An x-ray examination of the alimentary tract by Dr. P. J.

Briggs showed no abnormalities at all, nothing being found which could point to the presence of a gastric or duodenal ulcer. A fractional test-meal showed slight hyperchlorhydria, and blood was present in some of the fractions.

It was decided to give the patient as full a diet as was compatible with regular examinations of the stools for blood, and to give him a course of intravenous injection of 5 per cent. peptone.

Improvement followed immediately after the first injection (0·3 c.c. 5 per cent. peptone). The melæna, which had been present for over a fortnight, stopped completely, but occult blood was found in the fæces until a week later. Ten injections were given at five-day intervals, the dose being increased by 0·2 c.c. each time. There was no reaction after any of the injections.

The hæmoglobin began to rise, and the pulse rate, which prior to the injections had never been below 88 with an average of 100, began to fall, and after the fourth injection had fallen to 78.

Epistaxis occurred on the day of the third injection, but it only lasted a few minutes and stopped spontaneously; former attacks of epistaxis had been difficult to control.

No blood was subsequently found in the stools, and the patient was discharged from hospital vastly improved.

During the two months which have elapsed since his discharge no recurrence has occurred, and the patient is perfectly well.

Commentary

The history of recurrent melæna for seventeen years without digestive symptoms except for a few days after the hæmorrhage had begun and without radiological evidence of ulcer appeared to exclude any organic gastric or duodenal disease. The history of recurrent epistaxis preceding the onset of melæna and its subsequent occasional return, together with the family history of a hæmorrhagic tendency, render it probable that the patient was suffering from a similar condition to that of Case I. The effect of the peptone injections was again sufficiently striking to make this form of treatment worthy of trial in similar cases, though in this instance sufficient time has not elapsed to show whether it helps to prevent recurrence as well as shortening an attack.

A CASE OF SEVERE PYLORIC OBSTRUCTION WITH VISIBLE PERISTALSIS OVERCOME BY MEDICAL TREATMENT

By L. J. BARFORD, M.B.

NEWLAND M., aged 55, was admitted to Clinical in February, 1925, in a prostrated condition, suffering from agonising pain in

the abdomen, and having vomited at least once and sometimes several times a day for the preceding three weeks. His history was that for the last year or so he had been troubled with gastric flatulence, the eructated wind having frequently had a foul odour. There had been no pain at first, but for the last few months there had been vague abdominal discomfort with occasional pain and vomiting. The pain had not been localised to one particular spot, nor had it been constant. Three weeks before admission the pain and vomiting got very much worse, sometimes as much as two quarts being brought up at a time. The pain was almost completely relieved by the vomiting. There had been considerable loss of weight during the last six months.

The patient was one of a family of large-proportioned persons, he himself being 6 ft. 6½ in. tall; his mother and one of his sisters had had gastric ulcer.

On the day of admission he vomited altogether six pints of a watery fluid. Examination revealed very marked visible peristalsis in the stomach, although the abdominal muscles were well developed. No lump was palpable in the abdomen, nor was there any particularly tender spot.

A fractional test-meal done the day after admission showed a large amount of resting juice, although he had had only a few ounces of fluid by the mouth and had vomited considerably; the resting juice contained blood, starch, sugar and fat which must have been derived from a small meal taken fifteen hours earlier. The test fractions showed that, though there was considerable delay in emptying, the acid curves were within normal limits. Blood was present in nearly all the specimens, and there was no bile in any of them up to the end of 2¾ hours. Starch and sugar were present throughout.

The fæces gave positive guaiac tests for occult blood; hæmatoporphyrin was also present with the spectroscope.

The stomach was x-rayed a few days later with the following preliminary technique. The patient was allowed nothing by mouth except a little water after 10 p.m. on the night before; on the morning of the x-ray examination the stomach was completely emptied and washed out by means of a stomach tube until the returning fluid was quite clear; the stomach was then again completely emptied by means of an evacuator. The x-ray examination by Dr. P. J. Briggs one hour after this revealed an ulcer of considerable size on the lesser curvature, 1½ inches proximal to the pylorus, with a constant spasm of the greater curvature exactly opposite; there was no sign of malignancy.

The duodenal cap filled readily, showing that there was no organic obstruction of the pylorus, the signs and symptoms being due to achalasia of the pylorus as opposed to a true stenosis.

In view of the chemical and x-ray evidence being in favour of a simple ulcer without organic obstruction and opposed to the purely clinical diagnosis of carcinoma of the pylorus, it was decided to attempt medical treatment.

The patient was given nothing but saline solution by rectum for three days so as to give the stomach a complete rest. He was then given the strict ulcer diet with the accompanying olive oil, alkalis, and atropine; the feeds were kept as dry as possible and fluids were given by the rectum, a pint a day. The stomach was emptied each night at 10 p.m. with an evacuator, the last feed being given at 7 p.m. This was done in order to overcome the dilatation of the stomach. All infected teeth were extracted.

The vomiting and pain ceased from the beginning. Rectal fluids were stopped after a week and more fluids given by the mouth.

During the first week the stomach contents at 10 p.m. ranged from one to two pints; it was never less than one pint.

At the end of a fortnight from the commencement of treatment a second fractional test-meal was performed; this revealed still some delay in emptying, but no blood was present in any specimen, and, what was perhaps more surprising, bile was present in most of them, though there had been a complete absence of bile in the first test-meal.

Treatment was continued; the nightly stomach evacuation showed the contents to be getting gradually less. The diet was made more ample, thin bread, fish and potatoes being added. At the end of a month the stomach only contained on an average four ounces at 10 p.m. Symptoms had completely disappeared, and there had been a gain of almost a stone in weight.

A second x-ray examination was carried out four and a half weeks after the first one, the same preliminary technique being adopted. All evidence of the ulcer and the spasm had disappeared, and the stomach was completely empty in six hours. The stools now contained no occult blood.

A test-meal consisting of a large amount of bread, fish, potatoes and eight stoned raisins given at 10 p.m. showed no residue twelve hours later. The visible peristalsis, which was repeatedly demonstrated during the first few days after admission, completely disappeared directly after the strict treatment began.

The patient was discharged from hospital six weeks from the time of admission, having gained nearly a stone in weight and being able to eat a good moderate diet. He was seen again in December; he was free from pain and had gained a few more pounds in weight.

Commentary

This case is of interest because it shows the importance of thoroughly investigating cases even where the diagnosis seems obvious from the purely clinical findings alone.

It is doubtful whether the condition could have been diagnosed so completely had it not been for the preliminary evacuation of the stomach before the x-ray examination.

It also shows that visible peristalsis in the stomach must not be regarded as an infallible sign of organic obstruction, but can be present where, as in this case, the obstruction is due to reflex achalasia of the pylorus. Dr. Hurst has seen at least three similar cases of complete recovery under medical treatment in spite of the presence of very marked visible peristalsis and of all the symptoms of organic pyloric obstruction.

POLYPOSIS OF THE COLON FOLLOWING ULCERATIVE COLITIS DISAPPEARING UNDER TREATMENT WITH DEEP X-RAYS

By J. G. KINGSBURY.

HENRY S., aged 46, was admitted under Dr. Hurst in August 1924, on account of severe diarrhœa, the stools being fluid and containing much blood and pus. A sigmoidoscopic examination on September 9 revealed the presence of severe ulcerative colitis. The patient was treated by intravenous injections of polyvalent antidysenteric serum, followed by lavage with tannic acid solution (2 gr. to 1 oz.), and during convalescence by an autogenous vaccine prepared from Morgan's bacillus No. 1, which had been isolated from the stools and which agglutinated in the patient's serum at a dilution of 1 in 50. The stools quickly became less frequent and contained less blood. On October 24 the sigmoidoscope showed considerable improvement, but large numbers of very small ulcers were still visible, though most were so small that they could only be recognised with the magnifying eye-piece. At the edge of some of the ulcers small sessile polypi, which were certainly not present at the previous examination, were observed. By the end of November the stools were normal. On the 28th the sigmoidoscope showed that all the ulcers had disappeared, many without leaving any trace, but others leaving faint but definite depressed scars. Numerous small sessile polypi were scattered over the whole of the mucous membrane of the ten inches accessible to the sigmoidoscope, the number being very much greater than on October 24.

A barium enema given in February 1925 showed no evidence of narrowing of the bowel, but small round translucent areas could be recognised in the descending colon, which may have been caused by the presence of polypi larger than those in the pelvic colon. The patient was now feeling perfectly well in every way. There were no intestinal symptoms and the stools were normal. Apart from the condition of polyposis which had developed, the mucous membrane of the bowel when examined with the sigmoidoscope appeared to be quite normal. As, however, there is a well-known tendency for multiple polypi of the colon to become malignant, and as local treatment was obviously impossible on account of their enormous number and apparently

widespread distribution, it was decided to try the effect of deep x-ray therapy. Dr. Watt gave the patient three exposures in the first week of March 1925. The patient then left the hospital, but returned on April 7 to be sigmoidoscoped. All the polypi had disappeared, though in a few places a slightly raised area of mucous membrane appeared to represent the place where some of them had been. On April 29 a further three x-ray exposures were made; and in June a sigmoidoscopic examination showed no trace of abnormality. The patient was very well, and was still delighted with his condition when last seen at the end of September.

The following details of the x-ray treatment have been supplied by Dr. W. L. Watt.

Apparatus used: symmetric.
Voltage: 210,000 volts.
Filters: zinc 0·5, and aluminium 8 mm.
First series, on March 2, 1925:

40 minutes to front.
30 ,, ,, side.
40 ,, ,, back.

Total dosage to colon = 50 per cent. of skin erythema dose.

Second series, April 30, 1925:

40 minutes to front.
30 ,, ,, side.
40 ,, ,, back.

Total dosage to colon = 50 per cent. of skin erythema dose.

Commentary

So far as we have been able to ascertain, this is the first recorded case of multiple polypi of the colon developing as a sequel of ulcerative colitis. It is also, we believe, the first recorded case of the complete disappearance of multiple polypi as a result of deep x-ray treatment. The case was particularly interesting, as the gradual development of the polypi as the ulcerative colitis healed and their extraordinarily rapid disappearance were watched with the sigmoidoscope.

THE RADIOLOGICAL EXAMINATION OF THE PELVIC CÆCUM AND APPENDIX

By P. J. BRIGGS, MA., Radiologist to New Lodge Clinic.

THE help of the radiologist is often sought in the diagnosis of lesions affecting the terminal ileum, cæcum and appendix. Many authorities now realise that chronic appendicitis ought never to be diagnosed unless the appendix, when visualised with the x-rays, has been found to be tender, the tenderness being strictly confined to the appendix and moving with it when it is displaced by the other hand. Early carcinoma of the cæcum and ileo-cæcal tuberculosis can only be diagnosed with the help of the x-rays. The existence of adhesions fixing the appendix or interfering with the normal evacuation of the terminal ileum can, apart from operation, only be recognised with the x-rays. So often, however, have adhesions been diagnosed by the radiologist when their presence has not been confirmed at operation that we are beginning to realise that their recognition is not after all so easy as it at first might appear to be.

The difficulty of diagnosing these various conditions is enormously increased when the cæcum is situated in the pelvis, as it is then too deeply placed for satisfactory palpation, and owing to the relatively small size of the pelvis the shadow of the appendix is likely to be hidden by that of the cæcum, which is itself confused with the shadow of the terminal ileum and of the rectum.

The importance of this can be gauged when it is recognised that, so far from being a pathological condition, a pelvic cæcum exists in something like 30 per cent. of normal adults.

In some cases the difficulty of examination is readily overcome, the cæcum being easily drawn out of the pelvis by manipulation under the screen. But more frequently this cannot be done, especially if it is deeply situated. It is certainly quite unjustifiable to regard the impossibility of bringing the pelvic cæcum into the right iliac fossa by simple manipulation as evidence of adhesions fixing it in the pelvis. As a matter of fact it is extremely rare for such adhesions to exist.

It is thus a matter of considerable importance to devise some means for bringing the pelvic cæcum out of its deep situation into the right iliac fossa, when, with the terminal

ileum and appendix, it can be much more satisfactorily examined. There are three methods available, which I have found of the greatest possible value. The first two were described some years ago by Dr. A. F. Hurst,[1] but they do not appear to have been widely adopted. The third, which is very valuable in cases of pelvic appendicitis, has, I believe, not been previously described, though we have used it in suitable cases for the past four or five years.

1. *Inflation*

Inflation of the rectum and colon with air is easily accomplished by means of a rectal tube attached by a glass connection to a rubber tube and bulb. The air is pumped into the colon during the screen examination, until either the result is attained or the patient complains of pain. After the examination the rectal tube is disconnected at the glass connection and the air is allowed to escape, so that further discomfort to the patient is avoided. The cæcum is generally at once raised by the distended rectum and pelvic colon. It draws the ileum up with it, apparent kinks are unravelled, and the appendix, which had appeared fixed, moves in every direction. The appendix is now easily palpated, and tenderness can be noted. Radiograms may be taken to show any abnormality in the outline or filling. Sometimes it is necessary to combine manipulation with this inflation, a partially raised cæcum being completely drawn out of the pelvis by abdominal manipulation.

Incidentally inflation gives clinical evidence of the presence or absence of appendicitis, as in Bastedo's test. Bastedo of New York showed that inflation of the colon normally causes diffuse discomfort in the lower abdomen, but in chronic appendicitis it causes considerable pain in the right iliac fossa and increased tenderness of the already tender appendix.

In the rare cases in which the appendix is not visualised with the x-rays after repeated attempts, and tenderness is found in its situation as judged from its relation to the cæcum, Bastedo's test is negative. This indicates that the mouth of the appendix is obstructed or obliterated, a positive Bastedo's test being due to actual distension of the appendix.

2. *Distension of the Bladder*

In this method the object is to get the bladder as distended as possible. The number of hours taken to attain this varies with the patient. Taking ordinary diet with the usual quantity of fluids, the best time for the examination is in the morning before the evacuation of the bladder has taken place. If this

is not convenient, then I would suggest any time after the sixth hour.

The effect is striking. If the pelvic colon and rectum are not filled with the opaque meal, the greater part of the pelvis is occupied by a translucent area having a rounded upper border. The cæcum is lifted to a height varying with the degree of distension of the bladder, and if the small intestine be not empty, it will be seen lying above and to the left of the translucency, the whole forming an arch over the bladder. Palpation is not so easily performed as with the air inflation of the colon owing to the fact that there is a somewhat inelastic tumour present in the pelvis. I find that this method affords as good a screen picture as the air inflation, and that radiograms are more easily obtained owing to the fact that the pressure is exerted over a limited area and not dissipated throughout the colon.

3. *Bimanual Manipulation*

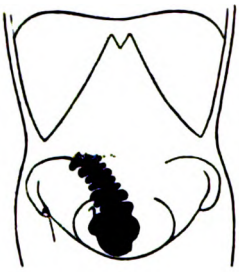
The symptoms in pelvic appendicitis are often anomalous, the usual reflex dyspepsia being associated with bladder irritation frequency and occasionally diarrhœa.

If the appendix be suspected, the diagnosis may be rejected by surgeons owing to the complete absence of tenderness in the right iliac fossa. Rectal examination shows that there is a tender point in front and to the right of the rectum. By examining the rectum under the screen when the cæcum is filled after an opaque meal, the tender point can be recognised to be the appendix, and the help given by *seeing* the appendix makes it quite easy for the finger in the rectum to *feel* it. The extent of mobility may be recognised and the presence or absence of adherence to the rectum or bladder.

If during the rectal examination the left hand of the observer is used to palpate the abdomen, the combination will often result in the cæcum being raised sufficiently high out of the pelvis to enable the appendix to be palpated through the abdominal wall in the ordinary way. This method of examination should be used in conjunction with the physician or surgeon in charge of the case, owing to the well-recognised dangers to the radiologist of exposure of the hands to direct rays.

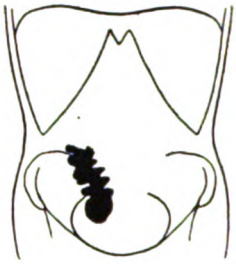
In conclusion I would like to give a brief summary of a case which I was given the opportunity of examining recently with Dr. Hurst at New Lodge Clinic, which illustrates the points I have already mentioned. The patient had an acute illness in India in 1921, and since 1923 has had intermittent attacks of pain in the region of the bladder and also epigastric discomfort.

In an attack he usually wakes at 2 a.m. with an urgent desire to micturate, but no relief follows emptying the bladder, the pain continuing till breakfast time and returning the next night. A diagnosis of chronic appendicitis had been rejected by two surgeons, as there was no right iliac fossa tenderness. A



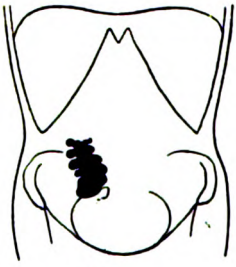
(*a*)

Showing position of cæcum and appendix in pelvis previous to manipulation. Lower pole turned outwards and upwards.



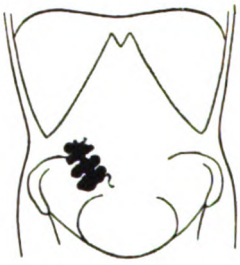
(*b*)

After injection of air into colon. Cæcum raised and straightened.



(*c*)

Cæcum and appendix raised by combination of air inflation and abdominal manipulation.



(*d*)

Cæcum raised into right iliac fossa by means of pressure exerted by a distended bladder.

FIG. 1.

Diagrams copied from actual radiograms of a case of pelvic appendicitis to illustrate the various methods of examination.

previous x-ray report stated that the cæcum was fixed in the pelvis.

After the usual opaque meal the cæcum was found lying low in the pelvis, but the appendix was not filled. Special technique for demonstrating the appendix was next employed, and it was now seen to be curled round the cæcum in an outward direction, but it was too low in the pelvis for palpation from the abdomen (Fig. 1 (*a*)). The colon was therefore inflated with air; the cæcum rose enough for the appendix to be palpated through the

abdominal wall; it was found to be tender (Fig. 1 (*b*)). After this the bimanual method was used: the appendix was visualised so that it became possible on rectal examination to guide the finger to it. It was then easy to feel, and it was found to be acutely tender; the left hand was then placed on the abdomen and used to draw the cæcum and appendix away from the finger in the rectum, the tenderness disappearing (Fig. 1 (*c*)) From these observations a diagnosis of chronic appendicitis was made.

REFERENCE

[1] A. F. Hurst: *Constipation and Allied Intestinal Disorders*, 2nd ed., London, 1919.

MYELOMA OF THE ULNA TREATED BY CURETTAGE AND AUTOGENOUS CANCELLOUS GRAFTING

By J. B. HANCE, O.B.E., M.B., Major, I.M.S.

THE treatment of myelomata by the method to be described was, as far as the writer can discover, first brought to the notice of the profession by Mr. A. H. Todd,[1] who employed it with conspicuous success in the case of a myeloma of the outer condyle of the femur. Few who were privileged to hear Mr. Todd's description of his case and to see his skiagrams can have failed to be impressed with the great possibilities of this form of treatment, in restoring both symmetry and function to the part affected, and, for the writer's part, it formed the inspiration of the treatment employed in the case hereunder recorded.

M.A., male, aged 40, applied to hospital on October 28, 1924, for treatment of a swelling on the ulnar side of the right forearm, in its lower third, extending to just above the wrist.

Of healthy cultivating stock, his history revealed nothing noteworthy except that his left leg had been amputated eight years previously at the seat of election for gangrene following an injury.

Three years previous to admission the patient had noticed a swelling in the lower third of the ulnar side of his forearm, which had slowly but steadily increased in size until its interference with the power and movements of his hand caused him to apply for relief.

On examination there was a swelling of the general size and shape of a goose's egg involving the lower third of the ulna. The hand was held pronated, supination being impossible, and attempts to effect it caused the patient a good deal of pain. Egg-shell crackling was elicited over the tumour in its posterior part, and the integrity of the middle of the inner aspect of the shell was doubtful. A radiogram (Fig. 1) revealed the distension and thinning of the shaft of the bone, with the bony septa typical of myeloma. A marked feature was the limiting reactionary compact bone at the upper pole, and the lower end of the ulna appeared also to be free.

Operation: 7.11.1924.—An incision five inches in length extending from the left anterior superior iliac spine back-

wards, parallel to and immediately below the outer lip of the iliac crest, was made, and carried immediately down to bone. The periosteum with the overlying muscles was stripped downwards with a rugine and strongly retracted, exposing an area of iliac bone some 4″ by 2″. With a broad gouge and hammer as much of the outer compact layer and underlying cancellous bone as possible was removed from this area and transferred

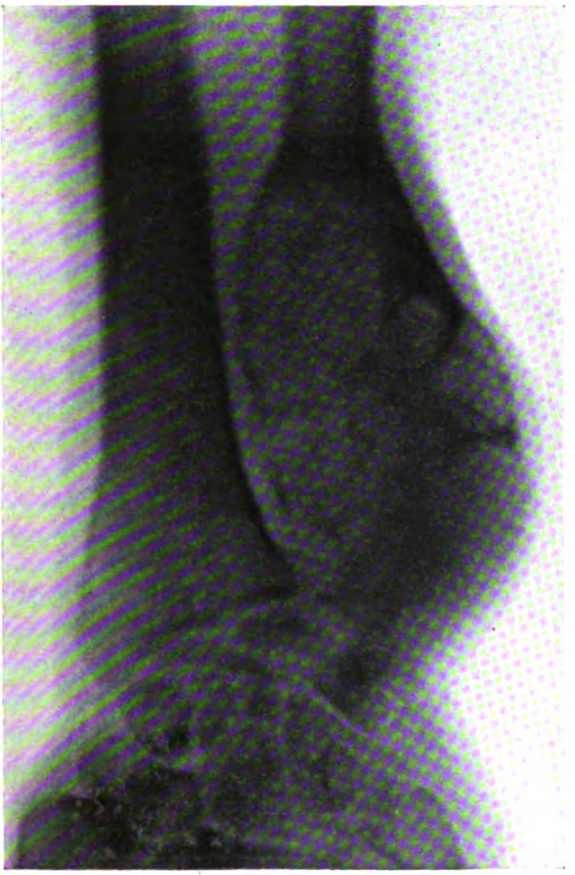


Fig. 1.

to a warm bath of autoclaved normal saline kept as near body heat as possible. The muscles and periosteum were then replaced, the cut edges of the former being united with three interrupted catgut retaining sutures, and the iliac wound was closed with Michel's clips.

Gloves, masks, and gowns were now changed, and during this interval the right upper limb was exsanguinated with an Esmarch's bandage and broad tourniquet.

An incision was made five inches in length along the inner

border of the right forearm between the flexor and extensor carpi ulnaris, extending from one inch below the styloid process of the ulna nearly to the middle of the ulnar margin of the limb. This was cautiously deepened till the ovoid swelling was defined, and it was seen that its inner central part to the extent of a sixpenny-piece was softened. The periosteum was next incised, in the line of the wound but "ringing" the softened area, and, with the overlying soft parts, stripped outwards and securely packed off with gauze to avoid future contamination with growth tissue. The inner side of the tumour was next incised at the softened area and the opening enlarged with scissors and nibbling forceps, till every bit of softened bony shell was removed. The tumour material was scraped out

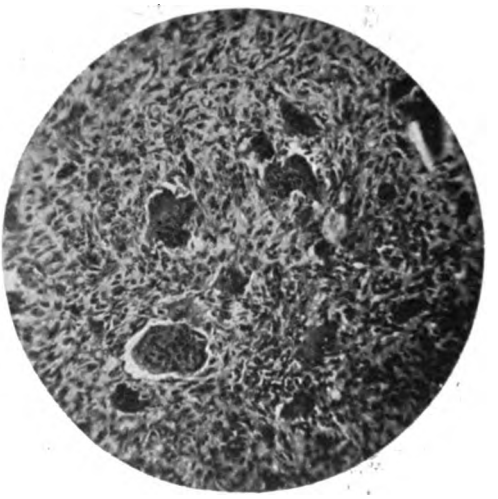


FIG. 2.

with a sharp spoon, and the whole of the inside of the ovoid cavity thoroughly and systematically curetted till every trace of tumour tissue had been removed. The opening into the tumour was then enlarged by removing the whole of the ulnar side of its shell, leaving an oval gap. The shell was found to be limited above by dense compact bone and below by a thin layer of similar bone overlying the articular cartilage. The interior of the cavity was next carefully swabbed out with pure carbolic. The excess of the latter having been thoroughly removed with absolute alcohol, the cavity was swabbed over with ether, dried with a stream of warm air, and the fragments of graft removed from saline and placed into the cavity, and the walls of the latter crushed down on to them. It was found that the graft was not sufficient entirely to fill the cavity, so further crushing was performed, the soft parts unpacked and allowed to fall over the gap in the bone,

and the wound closed by Michel's clips. Dressings having been applied, the hand was fully supinated and firmly bandaged on to a zinc " cock-up " splint, the tourniquet was removed, and the patient returned to bed.

During the whole operation, Lane's technique for bone operations was rigidly adhered to, and the gloved hand never touched the wound. Instruments which had touched myelo-

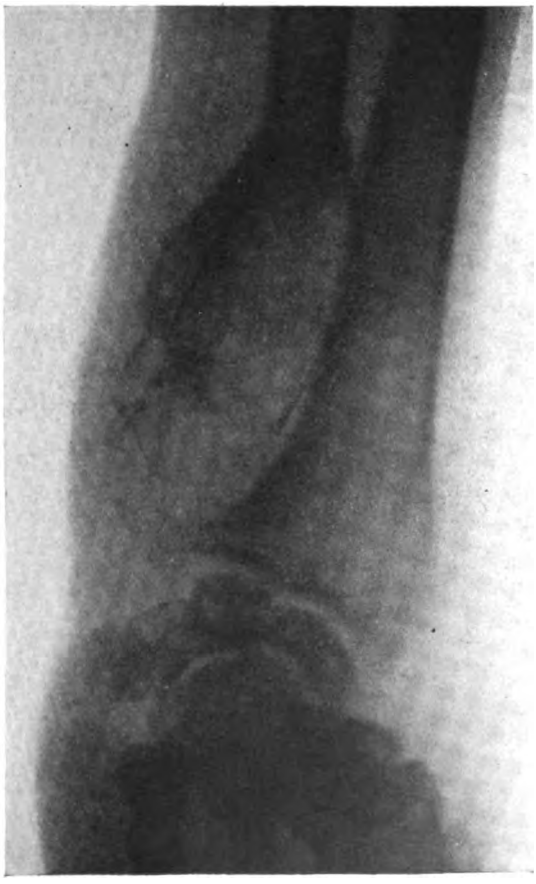


FIG. 3.

matous tissue were discarded after use, and fresh instruments used after the sterilisation of the tumour cavity. The tumour material was despatched to the Central Research Institute at Kasauli, where, by kind permission of the Director, it was examined by Major L. A. P. Anderson, I.M.S., whose report is as follows : " The sections of the material show the typical structure of a myeloma." Fig. 2 is a microphotograph showing the appearance of this tissue on section. To enter into any discussion of the histology would, after the work of Burlend

and Harries, be invidious; more especially as the method of removal of the myelomatous material precluded any serial sectioning. Suffice it to remark that study of these sections offers striking confirmation of the observations of these authors as to the appearance and staining reaction of the giant-cells and the genesis of the spindle cells.

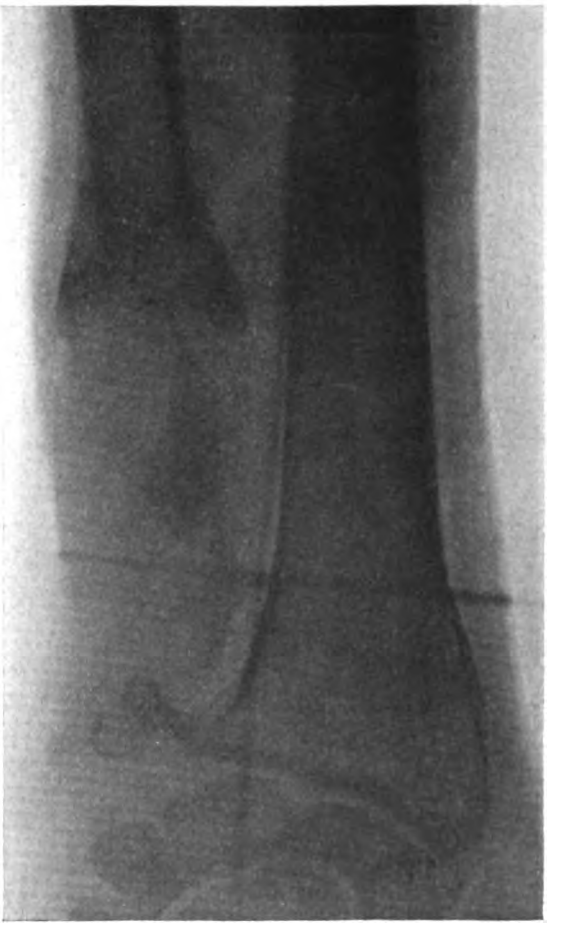


FIG. 4.

Hæmorrhage was controlled by firm bandaging, which was cautiously loosened after twenty-four hours, and movements of the fingers were encouraged from the start. Clips were removed in two stages on the eighth and tenth days. On the latter occasion a little serous discharge from the centre of the wound occurred. Forty-eight hours later when next dressed there was none, and the wound healed by primary union. Gentle massage was then instituted and finger movements increased with daily active and passive movements

of the wrist. After a month the splint was removed for an hour daily and active movements progressively increased, with special attention to pronation and supination. After two months the " cock-up " splint was replaced by a straight splint to the wrist, and continuous active movements and performance of light tasks encouraged; and the patient left hospital with free wrist movement and wearing a wrist splint on January 24, 1925.

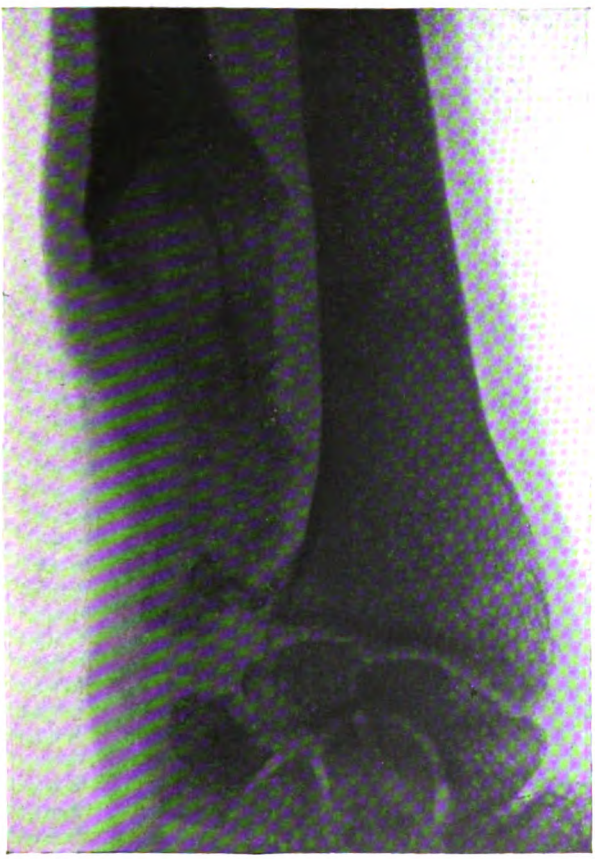


FIG. 5.

After four months all splinting was dispensed with, and the patient advised to use the hand for light tasks. Radiograms (Figs. 3 to 7) taken at one, two, three, five and seven months after operation respectively show the progress of the graft. Especially noteworthy is the tendency shown by the new bone progressively to revert to the normal outline, thereby bearing out the graphic phrase of Sir Arbuthnot Lane, that "the skeleton is the crystallisation of lines of force." At seven months after operation the patient reports that the

right hand and arm is but little weaker than the left, and, as shown in Figs. 9 and 10, he has full pronation and supination, while an idea of power may be gained from the fact of the ease with which he is holding up a large earthenware pot full of water.

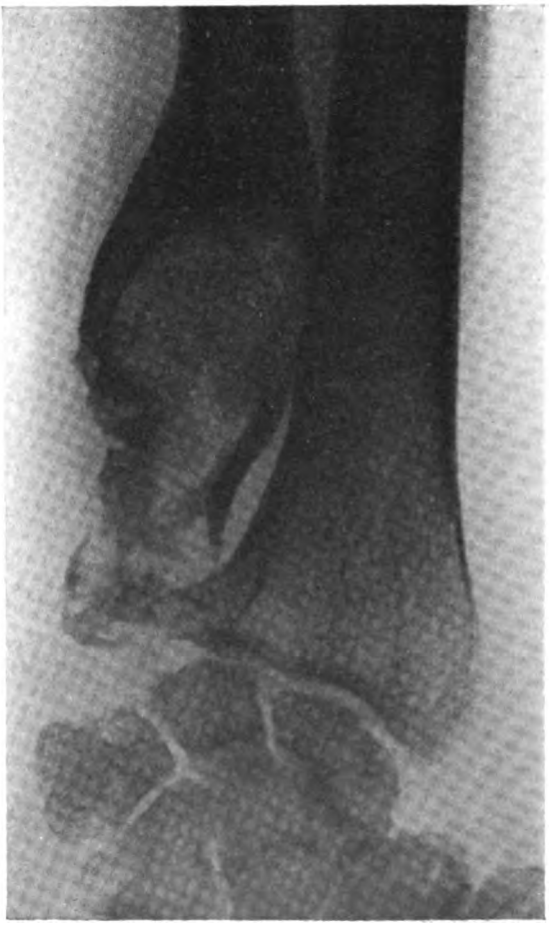


FIG. 6.

REMARKS

It would appear that this form of treatment of myeloma has not yet received the attention which it deserves. Diagnosis of the condition having been established, conservative treatment is the obvious indication. Rowlands and Turner [2] quote Mosetig and others as having extensively used various fillings such as iodoform wax for the filling of bone cavities, but only

in cases of caries, and their criticism of these methods are that "most of them have proved failures." These authors make no reference to this treatment being applicable in myeloma. Burlend and Harries,[3] in a most instructive article, describe the treatment of a white myeloma by a boiled heterogeneous graft. Such, however, according to Trethowan,[4] neither live

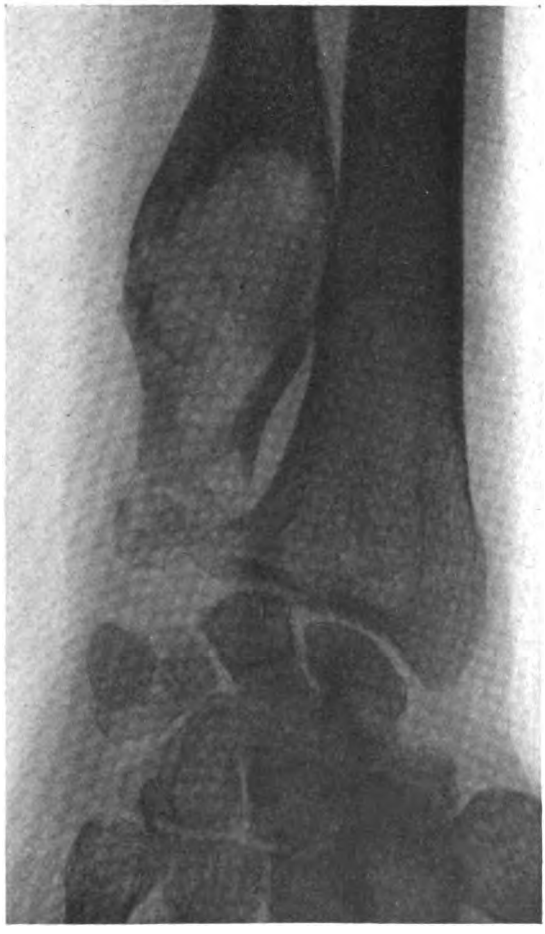


FIG. 7.

nor proliferate, acting merely as a scaffolding—a contention substantiated by the radiographs published by the two former authors. Carson [5] refers pessimistically to the treatment of myelomata by homologous grafts from a "recent amputation or from a corpse." The pessimism prevailing as to the success of wax fillings, heterogeneous and homologous grafts is scarcely surprising in view of the fact that they are inert substances,

which, if inserted with due regard to asepsis, can at best but act as scaffoldings. Trethowan,[6] in laying down the principle governing the grafting of bone, lays stress on the advisability of an autogenous graft, but the same author states that the breaking-up of the graft has no advantage. Todd's case, cited

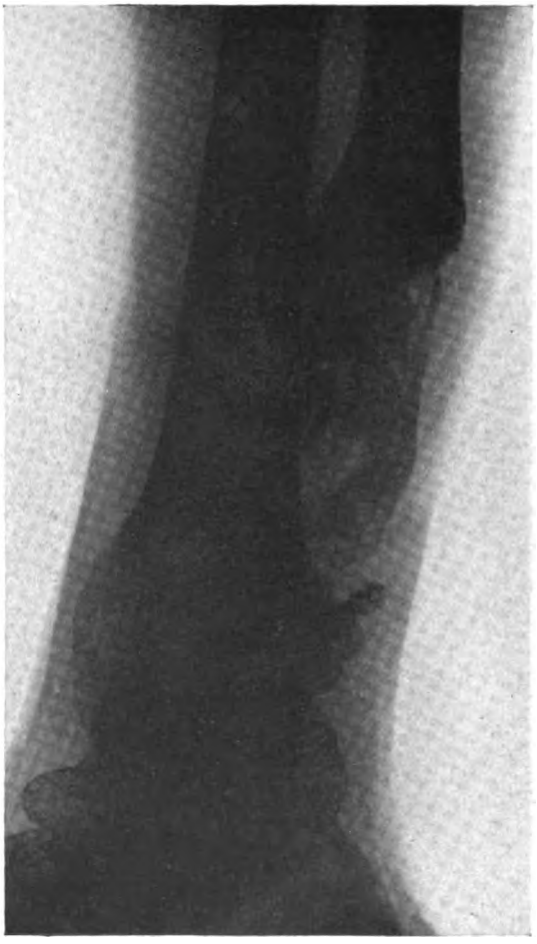


FIG. 8.

In semi-pronation, illustrating the approximation of the line of new bone to the normal from this aspect.

above, and the one here recorded, on the other hand, would seem to suggest that this method, which is the essential of cancellous grafting, has the very definite advantage of (1) providing the maximum number of osteophytes possible, and (2) providing a malleable medium for the "lines of force"

generated by carefully graduated active movements of the part when protected by accurate splinting. The results of these advantages are seen in the earlier return of function and the greater degree of symmetry obtained by this method than by the grafting of compact bone. Todd has shown that no evil effects attend the removal of even large quantities of the iliac bone. In the case here recorded this question in view of the previous amputation hardly arose.

Summary

The suggestions put forward are:

(1) That the treatment of myelomata by curettage and autogenous bone grafting is worthy of a more extended trial, and, provided rigid asepsis is observed, holds out the promise of good results.

(2) That cancellous grafts, as malleable bone-forming media, tend, in association with graduated movements and accurate splinting, to an earlier restoration of function and symmetry than do grafts of compact bone.

Fig. 9.

Fig. 10.

I am indebted to Lieut.-Col. S. R. Christophers, C.I.E., I.M.S., Director, and the officers of the Central Research Institute, Kasauli, for the pathological examination and the microphotograph of the tumour material.

NOTE BY ALAN H. TODD, M.S.

THE case to which Major Hance refers is that of a baker's roundsman, aged 24 years, who sustained what was at first thought to be an injury of the external semilunar cartilage of his right knee, in consequence of a fall when going down some steps whilst carrying a basketful of loaves on his head. On x-ray examination, however, it was found that there was a large myeloma occupying the whole of the outer condyle of the femur, and extending down to, but just not involving, the articular cartilage. The clinical characters of the case suggesting a diagnosis of myeloma, it was decided to make an attempt to preserve the structure and functions of the condyle, and so of the knee-joint, since the cavities left after erasion of the tumour would have been so large as to have left practically no alternative to amputation. Therefore after thorough erasion of the tumour and cleansing of the cavity by means of pure phenol followed by alcohol, the whole cavity was filled with bone-chips taken from the ilium; a large piece measuring 3″ × 3″ was used, taken from the whole thickness of the bone, after sub-periosteal dissection of the muscle from either aspect of the bone. In order that an osteogenetic surface might be presented, from which proliferation of bone might easily take place, these pieces of the ilium were split in two and packed firmly layer upon layer, into the cavity in the femur, and the whole mass was then firmly impacted by means of several blows from a heavy hammer. This was done in the hope of fixing the transplants of bone firmly in place, so that they might readily acquire a blood-supply and not become isolated in space in consequence of movement. The wound healed by primary intention, and all the grafts "took"; for about a year afterwards the patient walked about in a weight-relieving calliper-splint, so that the weight of the limb should not crush the newly-forming bone, with which the cavity gradually became obliterated. The operation was performed in 1922, and in 1923 the patient was working and had a full right angle of movement at the knee. He continued at work until April 1924, when he complained of a certain amount of pain behind the knee. On re-examination it was found that there was a small recurrence of the growth upon the posterior surface of the femur, so, taking into consideration the further period of incapacity that would result from a further conservative operation, the risk that the growth was, in fact, a sarcoma and not a myeloma, the anatomical difficulty of obtaining efficient access to the growth in its new situation, and for other reasons, it was decided to amputate the limb. This was done in May 1924, and no recurrence of the

growth has since taken place. The specimen is to be seen in the Museum of the Royal College of Surgeons of England, and it is interesting to find that the greater part of the newly-formed bone has been replaced by growth. Mr. T. W. P. Lawrence has examined sections of the growth and has expressed the opinion that it is definitely sarcomatous in nature; that is to say, it is to be regarded rather as a mildly malignant sarcoma containing giant cells than as a non-malignant myeloma.

This unfortunate end-result, however, in no way detracts from the value of the operation for a case of pure non-malignant myeloma, and indeed the efficacy of the method was proved by the fact that the grafts consolidated and enabled the man to do his work in comfort for a year or more after the operation.

About a year later another case presented itself, in which the method was again put to the test. D. P., a lady of 28 years, complained of aching in the right hip, and upon x-ray examination it was found that the whole of the great trochanter, the outer portion of the neck of the femur, and the uppermost portion of the shaft, were occupied by a large cyst, produced by fibro-cystic disease in the bone. The fibro-cystic material was curetted out, and the cavity was packed with fragments of bone taken from the ilium exactly as in the former case. All weight-bearing was prevented during the stage of consolidation of the graft, and at the present time the patient is going about as usual without any splint, doing her household work and looking after a family.

As regards the technique of the operation, one may remark that it is better not to remove the anterior superior iliac spine, as this may result in relaxation of Poupart's ligament; but there seems to be no great advantage in preserving the crest of the ilium, since the gap caused by the removal of the bone is rapidly filled up by a fresh mass of dense fibrous tissue which acts efficiently as a substitute for the bone. It is not suggested that the implantation of fragments of bone is to be employed in preference to transplantation of complete autogenous bone, where inlay-grafting of this material is applicable, *e.g.* in the repair of fractures of the long bones; in such cases the mechanical stability of the tibial intact graft is greatly to be preferred. But where, as in the present cases, a large cavity has to be filled, and it is impossible to obtain a mass of autogenous bone large enough to do this, the utilisation of a number of fragments of cancellous bone seems to offer the greatest possible advantages.

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[5] H. W. Carson: *Operative Surgery.*
[6] W. H. Trethowan: *loc. cit.*

DENTAL EDUCATION IN THE UNITED STATES AND CANADA

By J. LEWIN PAYNE, O.B.E., L.D.S. R.C.S., Dental Surgeon to Guy's Hospital.

Dental Education in the United States

When comparing the education of dental students in this country with that which is commonly found in America, it is necessary to bear in mind that there are certain fundamental differences in the aims, requirements and methods of administration in each country. In the first place dentistry in America holds quite a different position in relation to the community from that which it occupies in our own country.

In America to-day medicine and dentistry are two distinct professions. The treatment of teeth and jaws has been put into a class by itself. The graduate of a medical school who has not graduated from a dental school is prohibited from practising dentistry in the United States. The medical man may practise on the nose, throat, ears or eyes but not lawfully upon the teeth, except that, in a few States, he is allowed to extract them.

Across the water dentistry has been looked upon as a highly mechanical department of the healing art, but not as an accredited part of medicine.

Divergence in teaching begins at the outset of professional study. The requirements for the preliminary education vary widely from those of medicine so that at the present time it is difficult for a dental student to take a medical degree or for a medical man to become a dentist.

We were informed that if a dental student wishes to become doubly qualified he would have to spend at least nine years over his professional education.

It is common knowledge that the average American is a convinced believer in the standardisation of his commercial products. He manufactures railway engines by the hundred, all copied exactly to a single pattern; he produces pieces of dental apparatus by the thousand; and he turns out his most efficient motor-cars literally by the million. So, too, the teaching in most of the dental schools is standardised. But, whilst this is so with regard to the students in each particular

school, there is, nevertheless, a greater variation in the standard of the different schools than is found in this country; also the tendency to specialise in one branch of practice is much more common than it is here.

The reason for this variation is that each State makes its own dental laws, and, until recently, there was no active co-ordination between the educational authorities of the various States.

America can boast of possessing the oldest dental school in the world, for the Baltimore College of Dental Surgery was established under a charter granted by the State of Maryland in 1839—twenty years before our first dental school was founded. It happened in this way: two prominent practitioners, Drs. Hayden and Harris of Baltimore, realising the growing importance of dental surgery to the community, sought, during the third decade of last century, to establish a course in dentistry at the University of Maryland, belonging to the State in which they resided. At that time the leaders in medical practice were unable to appreciate the important relationship between dental disease and the health of the individual, and so their request was refused; but, failing in this undertaking, Hayden and Harris at once set about to form an independent Dental School, which was known as the Baltimore College of Dental Surgery. Here the distinction between dentistry and medicine began to assert itself, and the gulf widened through succeeding years.

Thus, early dental education in the United States, as in this country, was left largely to its own endeavour. Dentists learned their technique in the workrooms of practitioners, and sometimes added to this training a course of lectures in anatomy, physiology, and materia medica.

Moreover, the education both of medical and dental students during last century was largely in the hands of proprietary institutions, which often were concerned more with the profits of the owners than in securing the best education for the students.

The dental laws of the various States (of which there are forty-five) differ in many respects, and in some advertising is tolerated. A dental degree from a university or dental school does not automatically qualify the graduate to practise dentistry.

The carrying out of dental laws and the conduct of examinations are in the charge of the State Board of Dental Examiners appointed by the governors of the State.

After a student has taken his degree, he must pass the examination of that particular State in addition, before he obtains permission to practise in that part of the country.

During a tour of under six weeks Mr. Parfitt and I paid visits to the following seventeen Dental Schools :

1. New York College of Dental Surgery.
2. Columbia University School of Dental and Oral Surgery.
3. The Evans Dental Institute of the University of Pennsylvania, Philadelphia.
4. Temple University Dental School, Philadelphia.
5. University of Maryland School of Dentistry and the Baltimore College of Dental Surgery.
6. Georgetown University Dental School, Washington.
7. Howard University Dental School, Washington.
8. North-Western University Dental School, Chicago.
9. Chicago College of Dental Surgery.
10. University of Illinois Dental School, Chicago.
11. University of Minnesota Dental School, Minneapolis.
12. University of Michigan Dental School, Ann Arbor.
13. Royal College of Dental Surgeons, University of Toronto.
14. University of Buffalo Dental School.
15. Harvard University Dental School, Boston.
16. Tuft's College Dental School, Boston.
17. Dalhousie University Dental School, Halifax, Nova Scotia.

At a few of these institutions we had only an opportunity of a general look round; at many we spent several hours watching the work of students and inquiring into the organisation and the methods of teaching; whilst at some we spent time enough to go carefully into the working of all the departments.

We also visited—

Jefferson Medical College, Philadelphia.
Johns Hopkins Hospital, Baltimore.
Washington University Medical School.
Mayo Clinic, Rochester, Minnesota.
Battle Creek Sanitarium.
Eastman's Dental Clinic, Rochester, New York State.
Forsyth Institution, Boston.

In the course of the last twenty-five years great changes have occurred in the dental schools of America, and one after another the leading universities of the country have made provision for the training of dental students.

Since 1921 the Carnegie Foundation for the Advancement of Teaching has been studying dental education in the United States and in Canada. All of the dental schools in these two countries have been visited by representatives of this splendid organisation, and inquiry was made at each regarding its

condition, aims, needs and opportunities. Some interim reports have been published, but the work is still in progress.

At the commencement of this study, in 1921, fourteen independent schools in the United States of America were partly proprietary in character and were conducted on a plane that was obviously commercial. Of that group two have been absorbed by dental schools in universities; one has become a new, integral part of a university; three have effected affiliations with universities that are expected to be initial steps to organic union. One has closed down. Thus the number of independent dental schools in the United States has dwindled since 1921 from fourteen to seven, of which only one continues to be proprietary.

This inquiry and the discussion which followed have encouraged general improvement in the quality of dental education in America. In 1924 the total number of dental schools in the United States was forty-three, and of these thirty-four are now schools of universities.

In 1922 there were 40,000 dentists in practice in the United States and 13,000 dental students in attendance at the schools. Yet it is said there is still need for a larger number of practitioners and a wider and more effective distribution. The five Canadian dental schools are parts of, or are closely affiliated with, universities, each of which has a school of medicine attached. There are 3,200 dental practitioners in Canada.

In 1921 only twenty of the fifty-one dental schools then existing in the United States and in Canada required a year of college work before admission to the first year class. In 1924 more than half of the whole number had made the college course compulsory, and in 1926 practically all the schools will require at least one year of such preliminary training. Ten of the schools will demand a two-year college course, whilst Montreal and Rochester have fixed three years as the minimum.

The various medical and dental schools in the United States are graded into classes A, B and C. Class A represents schools which meet and maintain the full requirements set forth by the Medical or Dental Educational Council. Class B represents schools which, in certain particulars, do not meet all of the requirements, but which, in the judgment of the Educational Council, will be able to do so within a reasonable time. Class C includes schools which cannot, in the opinion of the Council, meet the requirements without extensive improvement and complete reorganisation, or which are conducted for profit to individuals or to a corporation.

The requirements for admission to most of the American dental schools to-day consist in a four-year course at an

accredited high school. After Matriculation dental education is divided into (*a*) the pre-dental course, or college work, and (*b*) the professional course. The pre-dental course at present is usually completed in one year. The subjects included in this course are—English, chemistry, general biology, and some of the following subjects : modern foreign languages, mathematics, physics, history, technical drawing, and shop practice. Further it is being urged in many of the best schools that the pre-dental college course shall be extended to two years and so place the preliminary education on an equal footing with that of medicine.

Thus the need of a more thorough general education, which will include a larger proportion of medical science, is being met by the efforts of those who are actively interested in raising the standard of dental education.

The ordinary professional course extends over four years. The year's work commences at the end of September and finishes at the end of May, occupying a period of eight months as compared with our ten-months hospital year.

Dental Education in Canada

The practice of dentistry in Canada is governed in each Province under the provisions of a Provincial Dental Act. In Ontario the affairs of the profession are administered in the manner of a public trust through a board of directors elected biennially by the licentiates residing within the Province. The corporate name of the profession in Ontario is the Royal College of Dental Surgeons of Ontario, and each licentiate becomes by virtue of his title a member of the College. The College exercises the dual function of teaching undergraduates and licensing candidates who pass its final examinations. The teaching function is carried on through the School of Dentistry, which was established in 1875. The Royal College of Dental Surgeons has been affiliated with the University of Toronto since 1888. The L.D.S. diploma and the D.D.S. degree are both granted by the same body.

Students of the Royal College of Dental Surgeons of Toronto are eligible to sit for any of the Examinations of the Dominion Dental Council of Canada, and the school is recognised by all *Class A* schools in America.

A candidate for admission must have matriculated in the Ontario University, or present a certificate of matriculation at an approved British or Canadian University, or a certificate accepted by the General Medical Council of Great Britain, or a degree in arts. The subjects are—English, history, mathe-

matics, Latin, physics, chemistry, and one of the following: Greek, French, German, Italian or Spanish (preferably French).

In 1921 a compulsory pre-dental course was established consisting of chemistry, physics, biology, English, French, hygiene, ethics, comparative dental anatomy and economics.

Courses are given in medicine and surgery; students are required to attend also one of the general hospitals with a surgeon during not less than twenty hours to see his clinical cases.

A higher degree, with the title of Master of Dental Surgery, is available for licentiates in the Province of Ontario of not less than five years' standing. The examination for this degree includes—operative dentistry, medicine, surgery, bacteriology, exodontia, anæsthetics, prosthetic dentistry, and a thesis of two thousand words upon some subject chosen by the Faculty.

Conclusions

Having referred to the general aspects of dental education, I would give this as my opinion of the American dental schools. The buildings of the best schools are more imposing, more commodious and better equipped than ours. The standard of technical work in both operative and prosthetic departments is high. The general organisation of the various departments and the record keeping is more complete than with us.

Further, a much closer check is kept on the attendance of each student, and the time that he gives to his work can be accounted for fully. If students do not work well at the outset, or if they show signs of being unsuitable for the profession, they are sent away during the first year.

On the other hand, in the past a lower standard of preliminary education has been accepted by the American authorities than would be allowed in this country, and that standard differs markedly from the requirements demanded of the students of medicine. However, all the best schools are striving for a two-years pre-dental or college course, and this should place the dental students on an equality with those taking medicine.

The teaching of general surgery, medicine, and general hospital practice appears to be more restricted than it is with us; and the standardisation of operative work, whilst it helps the weaker student, may cramp the efforts of the more brilliant man.

There is a tendency to specialisation early in the career of a practitioner, which may limit his outlook and lead to deficiencies when called upon to make a diagnosis.

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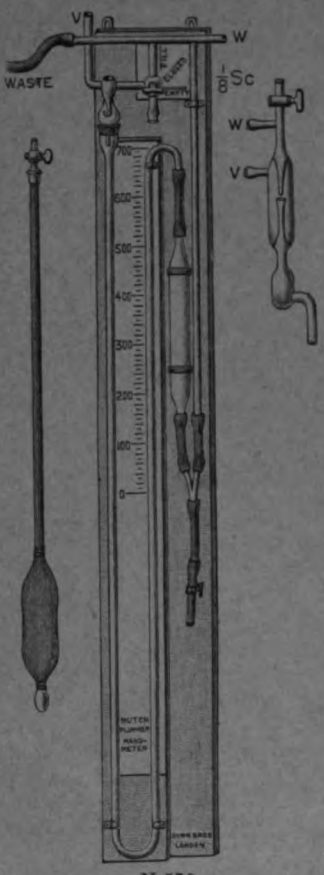

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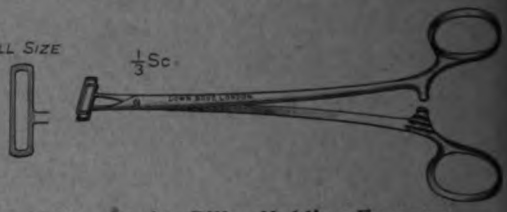

N 567 **Muck's Pillar Holding Forceps.**

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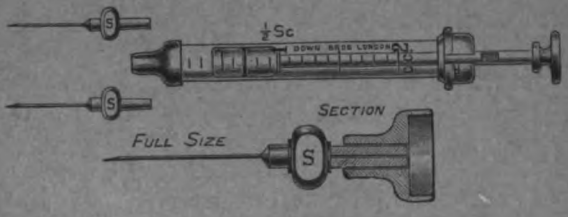

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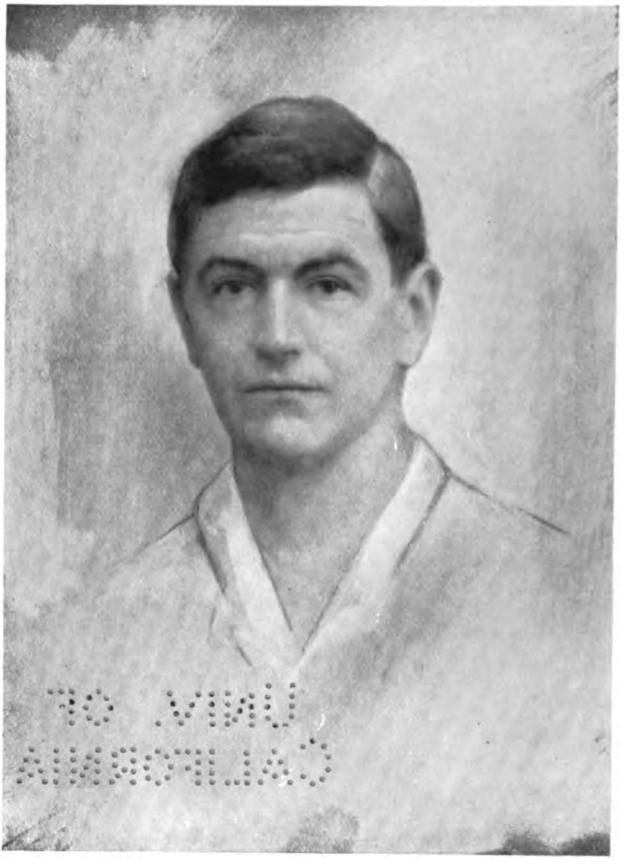

G. H. Hunt

IN MEMORIAM

GEORGE HERBERT HUNT, M.A., M.D.Oxon., F.R.C.P.

Physician to Guy's Hospital

In the death of George Herbert Hunt, Guy's, and with Guy's all those interested in English medicine, must mourn the death at the early age of forty-one of one whose work on the physiology and pathology of the heart had marked him out as a scientific clinician, who would some day rank among the most distinguished physicians of his time. But Hunt's death means much more than this. His colleagues have lost in him not only a dear friend, but a man whose devotion to duty and uprightness of character were an inspiration to all. And students will miss the privilege of learning from a teacher, whose gift of imparting knowledge and high ideals should have been an asset of incalculable value to his school and hospital for twenty years to come.

George Herbert Hunt was born on April 9, 1884, at Bickley in Kent, the only son of the late G. S. Hunt. At his preparatory school his head-master wrote of the " quiet influence for good " he exerted on those around him, a characteristic he maintained throughout his life. He continued his education at Rugby and at Christ Church, Oxford. Whilst an undergraduate he helped to carry out an original piece of research on the excretion of urine in a healthy man, immediately after one kidney had been removed on account of an injury incurred whilst playing football. At the end of his fourth year, in 1907, Hunt gained a second-class in the final honour school of physiology. One of his examiners informs me that he might have gained a first, had he not been in such pain during the examination as a result of a dental abscess that he had thoughts of giving up before the conclusion and claiming an " ægrotat." Sir William Osler, in a letter written at this period to a friend at Guy's, said, " You are in luck at Guy's. Look out for Hunt. He is an ideal man for your staff."

After doing the usual clinical appointments, Hunt became house-physician to Dr. Lauriston Shaw in 1911. He found time to help in the neurological Out-patient Department, and published a valuable note on the results of treatment of syphilitic disease of the central nervous system with salvarsan, which had only just become obtainable in England.

Having finished his term as house-physician, Hunt was appointed medical registrar as a matter of course. Though somewhat shy in manner, he was at once recognised as an excellent teacher. He obtained his M.R.C.P. in 1912 and was elected F.R.C.P. in 1919.

At this period the pioneer work of Sir James Mackenzie in cardiology was beginning to receive tardy recognition in London, but very few physicians had trained themselves to apply the new methods he had introduced to practical uses. Except for the investigation of a case of auricular flutter in 1908 with the aid of a polygraph, bought specially for the purpose by the house physician in charge of the case, little interest had been shown at Guy's in modern cardiological research. Hunt was quick to realise that the work of Mackenzie would in the next few years revolutionise our knowledge of heart disease, and he decided to make himself familiar with the new methods. In 1913, the year in which he was appointed assistant physician to the hospital, he published a paper on "Four Cases of Heart Block," and he showed a case of complete heart block and another illustrating the prognosis of extra-systoles before the Clinical Section of the Royal Society of Medicine.

The following year he published "Some Observations on Paroxysmal Tachycardia" and a paper on "Some Common Forms of Cardiac Irregularity." His interest in heart disease was maintained until his death, and he was prominent among the young generation of physicians, who, under the inspiration of James Mackenzie, gave British cardiology the leading position it has held in the last fifteen years.

Shortly after the outbreak of war Hunt went to France with the 1/2 London Casualty Clearing Station. In the early summer of 1915 attention had been drawn to a type of fever occurring in the British Army in France, in which two periods of pyrexia were separated by a normal interval. The disease was observed most commonly among officers and men living near the trenches, and it soon became known as trench fever. In November, 1915, Hunt published, with Major A. C. Rankin, an admirable account of thirty cases which had been under their care; this excellent piece of clinical observation proved of great value in leading to the wide recognition of the disease, not only in France but also in other theatres of war. It is interesting to note that, though equally prevalent in the other armies, the disease was not described in French or German literature until 1916. In that year, with J. W. McNee, Hunt published further observations on trench fever, in which it was shown that the same disease occurred in a more prolonged

intermittent form. In 1915 he was mentioned in despatches, and in 1919 he gained the rank of Brevet-Major.

After a period of service with the 25th General Hospital in France, Hunt joined the Royal Military Hospital, Devonport, in 1916, from which he was transferred to the Royal Victoria Hospital, Netley, in 1917. Here he organised a department of physical training for cases of so-called D.A.H. (disordered action of the heart). Hitherto they had been treated as cardiac invalids, and the recognition of the functional nature of the condition and the appropriate treatment by graduated exercises had a great effect in diminishing a very serious source of invaliding.

In 1917, after he had carried out some preliminary investigations in the R.E. experimental school at Porton, Hunt was transferred to Cambridge, where among more congenial surroundings he was given an opportunity of doing work of the greatest practical value in co-operation with Barcroft and others on the late effects of gas-poisoning.

I am indebted to Professor Barcroft for the following note about Hunt's work during this period :

"Captain G. H. Hunt joined me in the summer of 1917. He had already done work of considerable interest on the convalescent stage of gas-poisoning. In association with Price-Jones he had observed the high red blood count which persisted after poisoning with pulmonary irritant gases, such as phosgene and chlorine, and had studied the treatment of these cases by graduated exercises.

"The question arose as to whether oxygen treatment was beneficial in the rather chronic cases of poisoning with pulmonary irritants. These cases often showed a marked polycythæmia, and it was argued that since want of oxygen caused an increase in the red blood count, administration of oxygen might abolish it. Of course this was no strictly logical sequence. It seemed more easy to test the matter at Cambridge than at Porton. A small ward containing three glass rooms was therefore put up in the Physiological Laboratory : of this Hunt took command, and in company with Price-Jones, Miss Thursby Pelham and Miss Dufton—now Mrs. Charles Wilson—he carried out a considerable volume of work, much of which was published later in the *Quarterly Journal of Medicine*.

"It very soon became apparent that oxygen treatment did reduce the red count to something like normality for the time being. The more difficult decision was that of the permanency of the cure. To arrive at any final statement on this subject would require much longer and more frequent

observations of the patients after they had been discharged than Hunt was able to carry out during the war. I think it may fairly be claimed that in some cases this treatment broke a vicious circle and placed the patients on the road to permanent good health. In almost every case there was at least temporary benefit; in very few it proved useless. At the end of the war a hospital for oxygen treatment on a larger scale was erected, but by this time acute pulmonary irritants had ceased to be used.

"In the course of these observations Hunt became interested in two collateral questions. Firstly, the best method of testing the physical efficiency of his cases, and secondly, the degree to which patients suffering from complaints other than gas-poisoning could be benefited. The former led him up to a system of measuring the degree to which persons became breathless on exercise and developed later into one of testing the pulse on similar lines: the latter led to the erection of an oxygen chamber at Guy's Hospital."

During this period he wrote papers on the treatment of patients suffering from the "effort syndrome" and of chronic cases of gas-poisoning by continuous inhalation of oxygen, on the late symptoms of gas-poisoning, and on a numerical measurement of dyspnœa. In 1920 he took an important part in the discussion at the Royal Society of Medicine on the therapeutic uses of oxygen.

On his return to Guy's Hunt at once began to apply the lessons of the war to civil practice. Though the oxygen chamber (which was built in Addison under the auspices of the Medical Research Council, which appointed him Honorary Secretary of the Clinical Uses of Oxygen Committee) hardly fulfilled his early expectations, the new methods of estimating the functional capacity of the heart and of treating cardiac insufficiency by graduated exercises proved to be of the greatest practical use. Largely as the result of the work of Hunt and his colleagues, simple means were devised for determining the efficiency of the heart, which have proved as valuable as the new biochemical tests of determining the efficiency of the kidneys and liver.

For the following note on this test I am indebted to Dr. E. P. Poulton:

"Hunt introduced the 'pulse ratio' in order to estimate the functional capacity of the heart. It was a modification of the old-established method, viz. measuring the time that it takes for the pulse to return to the resting value after a given exercise. He and Professor Pembrey published in the *Guy's Hospital Reports* curves which illustrated the fallacy of the

latter method. The pulse ratio was worked out by Hunt in co-operation with other members of the Medical School, and the results are given in full in various papers in the *Reports*. To obtain the pulse ratio the pulse is counted during the first two minutes of rest after exercise is completed, and this number is divided by the pulse counted for one minute while the patient was sitting at rest before the exercise. An exercise is chosen of such a degree of severity that the ratio works out at 2·5. The efficiency of the individual is obtained by comparing this degree of exercise with the degree of exercise that has been found to produce a pulse ratio of 2·5 in the athlete. The exercise consists of stepping on and off a stool 13 inches high, for three minutes. In one subject, who was in very good training for boxing and football, after 30 steps a minute the pulse ratio was found to be 2·24. When he did the exercise 36 times a minute the ratio was 2·58. Interpolation between these values showed that an exercise of 34·6 times per minute would give a pulse ratio of 2·5. This result was taken as 100 per cent. and the efficiency of other people calculated in relation to it. If it is required to test a man with no obvious disease, it is best to start with an exercise of 18 steps a minute, and if this produces a pulse ratio below 2·5, the test is repeated at 24 steps a minute. If the pulse ratio now comes out above 2·5, interpolation will give the number of steps corresponding to a ratio of 2·5. Supposing that this is 20 steps, the efficiency will be $\frac{20 \times 100}{34{\cdot}6}$ or 57·8. If a patient has obvious cardiac disease a low rate of exercise must be chosen at first, such as 6 or 12 steps a minute.

"A strong point in favour of the pulse ratio is that with the same individual it remains fairly constant, even though the resting pulse may vary from day to day. This was tested by producing a rise in the resting pulse rate by means of a Turkish bath and then carrying out the exercise.

"However, the pulse ratio, like many clinical tests, must not be used without taking other circumstances of the case fully into account, and this was fully realised by Hunt. One disadvantage is that if a patient has a high resting pulse from cardiac disability, his efficiency will be found to be less than would be expected from the pulse ratio test, but a high resting pulse is itself a sign of cardiac disability. The main use of the pulse ratio is to determine the cardiac efficiency in patients whose pulse rate is normal. It is also a curious fact that when very severe exercise is taken, such as running a mile, the pulse ratio is found to be higher in the athlete than

in the unfit person, so that the test must be carried out with the mild exercise described above.

"Thus it will be seen that the pulse ratio test is not entirely free from objections, though it is probably the most valuable single test of cardiac efficiency that we possess."

In the summer of 1922 Hunt discovered that he was suffering from malignant disease. When the diagnosis was confirmed, he made all arrangements for immediate operation, but with rare courage continued his hospital work and took part in a golf match during the few days which elapsed before he went into Bright. Though he never regained his former strength, the immediate result of the operation was satisfactory, and when three years passed without any sign of recurrence, his friends began to hope that the disease had been completely eradicated.

From his return to activity in the autumn of 1922 until six weeks before his death Hunt worked with all his old enthusiasm. During 1923 he published papers on intermittent precordial pain and on the results of tonsillectomy in acute rheumatism, and in the same year in conjunction with J. M. H. Campbell and E. P. Poulton he continued his investigations on dyspnœa, which were embodied in a very important paper on "The Blood Gases and Respiration in Disease with reference to the Cause of Breathlessness and Dyspnœa."

In 1925 he was appointed full physician. He continued to superintend the medical work of the Massage Department, the high reputation of which is largely due to his sustained interest in everything and everybody connected with it since its foundation in 1913. He had early realised from a study of the text-books on massage and medical gymnastics that a large amount of careful investigation was required in order to test the truth of much of the current teaching, especially in connection with diseases of the heart and lungs.

In 1913 he tested the effect of active exercise on the blood pressure in rheumatic heart disease, but gave this up as the results proved to be of little or no value. He then proceeded to work out the effect of exercise on the pulse rate, taking for his controls the normal pulse of athletes in training among students at Bedford College and Guy's Hospital, and of people leading sedentary lives; his results were published in the *Reports* in 1922.

In 1919 he supervised an investigation into the effects of so-called local heart treatment. His early scepticism as to any physical effect on the heart produced by local massage was justified by the results of the tests, which were published in

the *Guy's Hospital Massage Association Report and Register* of 1920.

In the *Reports* for 1925 he published two important papers on "Massage and Remedial Exercises in Diseases of the Circulation and in Diseases of the Lungs and Pleura." In them the subject is discussed from a scientific as well as a practical point of view, and they mark a new era, at any rate in Great Britain, in the application of massage and exercises to the treatment of thoracic disease. Hunt had intended that they should form part of a series, which he would write in conjunction with various colleagues, and provisional arrangements had been made for their republication in book form under his editorship. It is hoped that his wish will still be fulfilled, as such a book would be a fitting memorial to the work he had done to establish massage and remedial exercises on a firm scientific basis.

"During the whole period of his connection with the Massage Department," writes Miss Angove, the Sister in charge, "he paid a visit once a week and gave valuable clinical demonstrations and lectures to the students in training. He took a personal interest both in them and in the staff, and his kindness, courtesy and never-failing help in all the many difficulties which arose during the rise of the Department from its origin to what it is to-day, will never be forgotten by any of those who had the privilege of knowing and working for him.

"Dr. Hunt's interest in the massage world was not limited to Guy's, for he frequently lectured to the members of the Chartered Society of Massage and Medical Gymnastics. In 1922 he gave a series of lectures on *Auricular Fibrillation* at a holiday course held at Reading by the Teachers' Association of the Chartered Society. In 1925 he was invited to become a member of the Council of the Society, and, although he had already more work than he was strong enough to do, he made every effort to attend the meetings and give the Society the benefit of his presence and valuable advice."

In 1924 he contributed to the series of articles published in the *Lancet* on "Modern Technique in Treatment" a very valuable article on the "Treatment of Functional Disorders of the Heart."

In the summer of 1925, though his health was indifferent, Hunt continued his hospital and private work with unabated vigour. He played as good a game of golf as he had ever done. He improved his handicap to 5, and won three competitions at Sheringham in bad weather on September 6. Nobody who came in contact with him during the last few months could

have guessed that he was a doomed man. At the end of October he appeared to enjoy the Guy's dance as much as anyone, and he played golf on November 9, though a few days later symptoms of a more painful character at last made it necessary for him to relinquish work. But to the friends who visited him he spoke with courageous optimism of his fibrositis and then changed the subject to Guy's and his work. A fortnight before his death, when an early end was clearly inevitable, he discussed hospital affairs with all his old interest, and even spoke of plans for the Tuesday combined rounds during Clinical in January. Happily his suffering was not prolonged and the end on January 9 was peaceful.

In 1915 Hunt married Miss Rosie Strauss. For her and for his two little girls the deepest sympathy of all who knew him will be felt. His chief interest outside his profession was music. He came from a musical family; he played the double bass in the Rugby orchestra, and his skill as a viola player was much appreciated at Oxford and Guy's, where he took a prominent part in the orchestra. His services were in great demand during the Christmas festivities. Dr. Poulton has recalled his power of singing difficult music at sight, both as a schoolboy in the choir at Rugby and later in the Bach Choir at Oxford.

He was an excellent golfer, and played lawn-tennis and hockey for his college. At Rugby he gave great promise as a chess player and won a cup in a match against Cheltenham.

Writing in the *British Medical Journal* "W. H. T." truly speaks of Hunt as "winsome, with a sweet smile and a gentle and kindly wit." A worthy son of Rugby, Oxford and Guy's, his character could not be better summarised than in the words of the Editor of the *Gazette*: "The peculiar affection and esteem which he inspired in all were the product of characteristics more subtle and less easily definable than those which commonly bring popularity. In Hunt's personality were felt a gentleness, a real humility, a sensibility to the feelings of others, and an undiscriminating courtesy, which inspired in his patients a confidence as deep and sincere as his manner with them was unaffectedly considerate. By the students he was regarded with an affection quite distinctive to himself. He was honoured and respected by those who knew him but distantly, under the formal conditions of hospital rounds or clinical lectures, as much as by his intimate friends. He was one of those rare characters which, all unconsciously, evoke the best in those with whom they come in contact, and in Dr. Hunt the hospital has lost a much-beloved figure whom it will be indeed hard to replace."

A. F. H.

HEART DISEASE AND PREGNANCY

By G. H. HUNT, M.D.

Edited by J. M. H. CAMPBELL, M.D., Medical Registrar, Guy's Hospital.

Introduction

DURING the last five years before his death Dr. Hunt was greatly interested in the question of the mutual influence of pregnancy and heart disease. He was trying to answer two questions. What is the probable effect of heart disease on pregnancy as regards the mother and as regards the child? And what is the immediate and ultimate effect of pregnancy on previous disease of the heart? He was also hoping to find some form of exercise tolerance test which would be a helpful guide to prognosis.

The latter inquiry was unfortunately incomplete, but I have included in the last table the " pulse ratio " for stepping exercises at different rates on many of the subjects here discussed. (Cf. G. H. Hunt and M. S. Pembrey: *Guy's Hospital Reports*, lxxi. 415, 1921.) Nothing further will be said about these results here, though they may be of value in comparison with some similar data for normal subjects and various other patients with heart disease.

As regards the two former questions, it is most fortunate that the inquiry was much more complete, and that Hunt had prepared some statistical tables for a clinical lecture on the subject. There were a few short notes and his conclusions with these tables. As these were based on a long series of 156 patients, and as the conclusions reached were very definite and amply substantiated by the statistics, it seemed desirable that they should be recorded, even if the paper had to be written by another hand.

In what follows the tables are entirely the work of Hunt (helped in the collection of the data by Mr. McNair, Mr. Cook and Mr. Lane Roberts). I have only made one or two minor corrections in accordance with some of his more recent data. The writing is unfortunately mine, but I have limited it to a description of how the statistics were collected, to an explanation of how the patients had been grouped, and to some short comments on the tables.

To Mr. A. J. McNair, Mr. Frank Cook and Mr. C. S. Lane Roberts I am indebted for permission to include the results on their patients and for their care in collecting many of the data. I specially wish to thank Mrs. Hunt for allowing me to make use of Dr. Hunt's note-books and records.

Source of these Statistics

The patients here described were collected from three sources.

(1) The larger number (98) were from the Ante-natal Clinic of Guy's Hospital under the care of Mr. A. J. McNair and Mr. Frank Cook. Their detailed history was obtained from the record of the Ante-natal Clinic, to which was added the result of their confinement in Guy's Hospital, or more commonly in their own homes under the care of the hospital charity.

Many of these patients were written to and examined by Hunt in 1925 one to five years after their first observed pregnancy. Notes were then made on their general condition and on the results of an exercise tolerance test. It is perhaps this group which is of special value, because all these patients had been originally examined and carefully classified by Hunt. It is only the patients of this group who are available for conclusions about the later result of pregnancy on their heart disease.

(2) The records of 31 patients from the wards of the City of London Maternity Hospital were also used, and the history of these patients and the result of pregnancy and labour on their heart condition were taken from the hospital report.

(3) The third group consisted of 27 patients from the wards of St. Bartholomew's and Queen Charlotte's Hospital. The account of these patients and of the effect of pregnancy was supplied by Mr. Lane Roberts. The statistics from these different sources were carefully considered, and the final classification and grouping given in the tables was made by Hunt, so that the method should be as uniform as possible.

Hunt purposely took cases from both in-patients and out-patients, as the former would only include heart failure and the more serious cases of heart disease, or complications of labour, while the latter would include a relatively small number of severe cases, and it would take a long time to collect sufficient data about these. The difference is well shown by the types of disease in the two groups. Of the 98 cases from the Guy's Hospital Ante-natal Clinic, more than half had disease of the mitral valve without any appreciable enlargement of the heart,

and less than a tenth had auricular fibrillation. Of the 58 cases from other sources (mostly or all in hospital), nearly a third had auricular fibrillation, and nearly all the others had valvular disease with definite enlargement of the heart.

Grouping of these Patients with Heart Disease

The patients examined have been divided into four groups.

I. Patients with mitral stenosis and regurgitation, alone or together, without appreciable enlargement of the heart. This comprises 60 out of the 156 patients, the great majority of these being from the Guy's Hospital Ante-natal Clinic. As about four-fifths of these patients had mitral stenosis, this group is referred to as "Mitral stenosis without enlargement of the heart," but it must be remarked that in nearly every particular the patients with mitral regurgitation reacted better than those with mitral stenosis; and those with mitral stenosis alone better than those in whom it was combined with mitral regurgitation.

II. Patients with mitral stenosis and regurgitation, alone or together, with definite enlargement of the heart. This comprises 49 patients, about equal numbers from the two sources (Guy's Hospital and elsewhere). This group is referred to as "Mitral stenosis with enlargement of the heart," as only three of these were without stenosis. Curiously enough, these three did quite as badly as the rest of the group, but the numbers are few, and one also had paroxysmal tachycardia. In this group the presence or absence of mitral regurgitation in addition to mitral stenosis did not appear to be of importance.

III. Patients with aortic regurgitation, with or without other valvular lesions. These were at first subdivided into (*a*) those with mitral stenosis and (*b*) those without mitral stenosis; but as the numbers were small and as there did not appear to be much difference they have been combined. This comprises 25 patients, only one-third being from the Guy's Hospital series. This group is referred to as "Aortic regurgitation."

In all the patients of these three groups the rhythm was regular; in practically all it was normal, but in 2419 and 5896 of Group II (see Table VII at end) there were attacks of paroxysmal tachycardia.

IV. Patients with auricular fibrillation. Most of these had mitral stenosis with or without regurgitation. This group comprises 22 patients, only one-third being from the Guy's Hospital series, and is referred to as "Auricular fibrillation."

Obviously these groups consist almost entirely of cases of valvular disease of the heart with or without associated myocarditis. Probably rheumatic infection was the etiological factor in the great majority, and cases of heart disease secondary to high blood pressure or lung disease and syphilitic myocardial disease appear to have been excluded, if they were encountered.

Among the rough notes, but not included in these groups or in the tables, are a certain number of patients with symptoms of heart disease or with bruits, in whom Hunt did not find any evidence of organic heart disease. In none of these was there any effect on the pregnancy or any subsequent deleterious effect on the cardiac patients. These few patients have not been referred to in more detail, as there is general agreement on the subject.

Results Obtained by this Inquiry

Fortunately Hunt had tabulated the results for a lecture (Tables I–VI), but unfortunately there are only very short notes of what he wished to say. To some extent the tables speak for themselves and strongly support the conclusions which he had formulated, but I am unable to reproduce much of the more valuable personal impressions which it was impossible to tabulate and difficult to include in short notes.

I have thought it best to include these notes which really serve to explain the tables which follow, though they only indicate the lines his lecture was to take.

" The danger of pregnancy is specially the increased nutrition and load; and of labour, the increased muscular strain."

" Practical experience shows that three things may happen to pregnant women with heart disease, and it is necessary to know which of these is the most likely: (1) they may die; (2) they may lose compensation and become permanently worse; (3) they may be none the worse."

" To the two questions, ' Ought a woman with heart disease to become pregnant? ' and ' If she does, what treatment should be adopted? ' varying answers have been given by different people. Among these, some deny that any useful prognosis can be given by examination of the heart."

" These varying opinions show the importance of more statistical evidence. Source of these statistics. Necessity for having in patients and out patients." (These last have already been discussed.)

The following tables illustrate clearly the main conclusions about the effect of heart disease in producing (1) death, (2)

failure of compensation and (3) increase of symptoms during pregnancy, and (4) its effects on the child. Shortly, where there was valvular disease but no enlargement of the heart, the disease of the heart had little effect on pregnancy. There were practically no deaths or cases of cardiac failure, but half the patients showed a temporary exacerbation of symptoms; nine out of every ten children were born normally at term.

TABLE I.

PATIENTS DYING DURING OR SHORTLY AFTER PREGNANCY.

	Total number of patients.	Deaths.	Percentage dying.
I. "Mitral stenosis without enlargement"	60	0	0
II. "Mitral stenosis with enlargement".	49	6	12
III. "Aortic regurgitation"	25	3	12
IV. "Auricular fibrillation"	22	8	36
All cases	156	17	11

TABLE II.

PATIENTS LOSING COMPENSATION DURING PREGNANCY, APART FROM THOSE FATAL CASES INCLUDED IN TABLE I.

	Total number of patients.	Compensation lost.	Percentage failing.
I. "Mitral stenosis without enlargement"	60	2	3
II. "Mitral stenosis with enlargement".	49	13	27
III. "Aortic regurgitation"	25	6	24
IV. "Auricular fibrillation"	22	12	54
All cases	156	33	21

TABLE III.

PATIENTS SHOWING NO CHANGE, OR ONLY A LITTLE WORSE, DURING PREGNANCY. (Percentages.)

	No change.	Rather worse.	Developing heart failure or dying (Tables I and II).
I. "Mitral stenosis without enlargement"	48·5	48·5	3
II. "Mitral stenosis with enlargement"	30·5	30·5	39
III. "Aortic regurgitation"	40	24	36
IV. "Auricular fibrillation"	5	5	90

TABLE IV.

EFFECT OF MATERNAL HEART DISEASE ON THE CHILD.

	Total.	Percentage born dead or miscarriage.	Percentage premature but alive.	Percentage normal and alive.
I. "Mitral stenosis without enlargement"	60	10	0	90
II. "Mitral stenosis with enlargement"	49	18	10	72
III. "Aortic regurgitation" . .	25	24	8	68
IV. "Auricular fibrillation" . .	22	36	14	50

In none of the tables is there much difference between the patients with mitral disease and an enlarged heart and those with aortic disease, so these can be considered together. In this group of enlarged heart with valvular disease nearly three patients out of each ten had cardiac failure during or just after pregnancy, and another one died. So of each ten nearly four had cardiac failure, sometimes fatal, three were slightly worse and three were unaffected; of each ten children, seven were born normally at term, one was premature and two were born dead. In every particular these patients reacted less favourably than the first group, but enormously more favourably than the last group to be considered. Possibly the prognosis given here is rather too bad, as a larger proportion of this group came from those who had been admitted to hospital.

In the rather smaller group of patients with auricular fibrillation, of each ten nearly four died, and another five had cardiac failure, so that only one out of each ten was not seriously affected. This is an appalling contrast with the other groups. The effect on the children was also bad, but not quite so bad as on the mothers. Only half were born normally at term, while of each twenty, three were premature and seven were born dead.

Another table showed the result of a previous breakdown of compensation. The mortality was not much greater, but

TABLE V.

EFFECT OF PREVIOUS BREAKDOWN ON SUBSEQUENT PREGNANCY.

	Number.	Percentage dying.	Percentage with breakdown during pregnancy.	Percentage slightly affected.	Percentage not affected.
Patients with previous breakdown . . .	18	17	50	27	6
Patients without any previous breakdown .	138	10	17	34	39

the number who again suffered from heart failure was enormously greater.

The results shown in Table III refer to the effect during and immediately after pregnancy, but in the Guy's Hospital series Hunt had followed the later results from one to five years after the first observed pregnancy. The result with the individual findings in most of the Guy's patients are shown in Table VII at the end. (I have not been able to find the full record of quite all the patients; *e.g.* Group I in Table VII shows 48 patients instead of the total 57; Group II, 20 instead of 26, and Groups III and IV the full number but with some data incomplete.)

Hunt had seen most of these patients in 1925, and in many cases had done an exercise tolerance test and recorded the "pulse ratio." The information seems least complete for Group III, but I think these patients had also been examined, as he gave the results in the following table.

TABLE VI.

PATIENTS WHOSE HEARTS WERE PERMANENTLY WORSE AFTER PREGNANCY.

	Total.	Percentage dying.	Percentage permanently worse.	
			Seriously.	Slightly.
I. "Mitral stenosis without enlargement"	57	0	0	23
II. "Mitral stenosis with enlargement"	26	8	8	40
III. "Aortic regurgitation" . .	8	12	12	?0
IV. "Auricular fibrillation" . .	7	14	14	28

The difference seems to be less than in most of the other points considered, but the two last groups are small, and it must be remembered that their heart disease was already serious before the onset of the pregnancy.

There are a few other points worth mentioning, which can be abstracted from the full details in Table VII on pages 142, 143. The average age of all the patients was 33, of those in whom compensation failed 29, and of those who died 34, so that there does not appear to be any significant difference.

There was a history of rheumatic fever in 30 and of chorea in 2, and no history was given in 44 (rest unknown), so that nearly half gave a definite history and the nature of the lesion suggested a rheumatic infection in practically all. On the average of all the cases the attack of rheumatism had been 20 years before, but the actual period was very variable; in the eight

TABLE VII.

Number.	Age.	Valvular lesion.	Enlargement of heart.	History of rheumatic fever and years ago.	Duration, in years, of symptoms (if known).	Previous breakdown.	Number of children.	Number of miscarriages.	Treated in hospital.	Condition of last-born child.	Symptoms of heart disease aggravated by pregnancy and labour.	Condition when seen in 1925.	Permanent deterioration produced by pregnancy.
3981	28	M.S. and M.R.	—	R.F. 18	—	—	1	—	—	S. *	—	Was at work	—
4003	28	,,	—	—	1	—	4	—	+	S.	+	E.T. 9 = 2·5 †	—
6113	44	,,	—	R.F. 34	—	—	9	3	—	S.	—	Good; E.T. 18 = 2·4	—
2727	43	,,	—	R.F. 24	5	+	10	1	—	S.	+	Breathless; E.T. 6 = 2·6	+
587	51	,,	—	R.F. 35	6	—	2	2	—	M.	+	E.T. 9 = 2·3	+
1508	43	,,	—	—	29	—	6	5	—	S.	+	Fair	—
4944	39	,,	—	R.F. 25	4	—	5	2	—	S.	+	Fair	+
3371	31	,,	—	Ch. 21	—	—	4	—	—	S.	+	E.T. 9 = 2·4	—
2968	32	,,	—	—	2	—	2	—	+	S.	+	E.T. 12 = 2·4	+
2073	34	,,	—	—	1	—	3	—	—	S.	—	E.T. 9 = 2·4	—
2397	28	,,	—	—	6	—	2	3	—	M.	—	Bronchitis	—
2180	32	,,	—	—	10	—	3	2	—	S.	+	E.T. 12 = 2·4	—
A.N.	29	,,	—	—	2	+	2	—	+	S.	+	Fair	+
2733	25	,,	—	R.F. 11	1	—	2	—	—	S.	+	E.T. 15 = 2·5	+
681	35	,,	—	—	2	—	3	3	—	S.	—	E.T. 12 = 2·3	—
2451	29	,,	—	—	—	—	2	2	—	S.	—	Fair	—
2805	31	,,	—	—	4	—	2	—	+	S.	—	Breathless; E.T. 9 = 2·3	—
2637	34	,,	—	R.F. 19	—	—	3	1	—	S.	+	Moderate; E.T. 18 = 2·5	+
849	24	,,	—	—	2	—	2	—	—	S.	—	E.T. 9 = 2·3	—
2210	30	M.S. only.	—	R.F. 23	1	—	6	1	+	S.	+	Good; E.T. 18 = 2·3	+
6905	38	,,	—	R.F. 12	—	—	2	—	—	—	+	Fair	—
863	30	,,	—	—	15	—	1	—	—	S.	—	Breathless; E.T. 9 = 2·2	—
1044	28	,,	—	Ch. 20	3	—	1	—	—	S.	—	E.T. 9 = 2·3	—
3687	30	,,	—	R.F. 14	14	—	6	—	—	S.	—	Fair	—
2684	33	,,	—	—	—	—	4	—	—	S.	—	E.T. 6 = 2·6	—
5017	31	,,	—	—	7	—	5	—	+	S.	—	E.T. 12 = 2·6	—
2197	31	,,	—	R.F. 26	12	+	1	5	+	D.	+ + +	E.T. 12 = 2·4	—
3567	30	,,	—	R.F. 25	—	—	2	—	—	S.	—	Good	—
244	31	,,	—	—	4	—	2	—	—	S.	—	E.T. 15 = 2·4	—
612	38	,,	—	R.F. 16	4	—	9	—	—	S.	+	E.T. 15 = 2·3	+
5644	39	,,	—	R.F. 30	30	—	4	—	—	S.	—	Bronchitis	—
440	32	,,	—	—	7	—	1	—	—	S.	—	E.T. 12 = 2·3	—
379	28	,,	—	—	5	—	1	—	—	S.	—	E.T. 15 = 2·6	—
1708	28	,,	—	—	10	—	2	1	—	S.	—	E.T. 15 = 2·4	—
993	30	,,	—	—	2	—	4	—	—	S.	—	E.T. 12 = 2·4	—
5083	28	,,	—	R.F. 15	4	—	5	—	—	S.	+	Fair	+
[illegible]	[illegible]	[illegible]	—	—	—	—	1	—	—	S.	—	Bronchitis	—

170	32	M.R. only.	—	—	6	—	—	—	—	S.	—	E.T. 15 = 2·2	—
697	34	,,	—	—	1	—	3	—	—	S.	—	Fair	—
859	43	,,	—	R.F. 35	—	—	13	1	—	S.	—	E.T. 15 = 2·7	—
3221	40	,,	—	—	4	—	7	—	+	S.	—	Fair	—
1836	25	,,	—	R.F. 15	—	—	3	—	—	S.	—	E.T. 12 = 2·4	—
4326	34	,,	—	—	2	—	3	—	+	S.	—	E.T. 15 = 2·4	—
827	25	,,	—	R.F. 18	—	—	2	1	—	S.	—	Good	—
4660	41	,,	—	—	2	—	5	—	+	S.	+ + +	Good	—
4336	34	,,	—	—	2	—	4	—	—	S.	+	E.T. 15 = 2·4	—
5378	41	M.S. and M.R.	+	—	—	—	8	—	—	S.	—	Fair; E.T. 12 = 2·5	—
888	43	,,	+ +	—	5	—	12	1	—	S.	+	Moderate	+
1471	39	,,	+ +	—	—	+	4	—	—	S.	—	Fair; E.T. 12 = 2·4	—
3364	28	,,	+ + +	R.F. 14	—	—	3	—	—	S.	—	Moderate	—
6289	38	,,	+	—	7	—	3	1	+	S.	+	Breathless; E.T. 9 = 2·2	+
2419	34	,,	+ +	—	5	—	7	1	+	S.	+	Poor; Paroxysmal tachycardia	+
4298	28	,,	+ +	—	15	—	1	—	+	P.D.	+ + +	Died 1924	+ + +
2474	44	,,	+ +	—	—	+	8	3	+	S.	+	Good	—
1882	33	,,	+ +	R.F. 19	7	+	6	—	+	S.	+	Moderate	+
1196	20	,,	+ +	R.F. 11	—	—	3	—	—	S.	+	Died	+ + +
5788	24	,,	+ +	—	2	+	1	—	+	S.	+ + +	Bronchitis	+
85	26	M.S. only.	+ +	R.F. 27	—	—	3	—	+	S.	+ + +	Died after statistics completed	+ + +
430	30	,,	+	R.F. 15	15	—	2	—	—	P.	+	Fair; E.T. 12 = 2·5	—
5339	31	,,	+ +	—	—	—	3	—	—	S.	—	Good; E.T. 18 = 2·4	—
1465	30	,,	+ +	—	4	—	7	—	—	S.	+	Moderate	+
209	38	,,	+ +	—	7	—	1	—	—	S.	—	Fair	—
412	40	,,	+	—	5	—	8	1	—	S.	+	Fair	+
2688	32	M.R. only.	+	—	—	—	8	1	—	S.	—	E.T. 18 = 2·6	—
3622	42	—	+ +	—	5	—	11	1	+	D.	+ + +	Fair	+
5896	35	—	+	—	5	—	7	—	+	S.	+	Paroxysmal tachycardia	+
R.	30	A.S. and A.R.; M.S.	+ + +	?	?	—	2	—	—	S.	+		+
F.	29	A.S. and A.R.	+ +	R.F. 22	—	+	3	—	+	P.	+ + +		+
I.	30	A.R.; M.S. and M.R.	+ + +	R.F. 15	4	—	1	—	—	S.	+	Poor	+ + +
M.	?	A.R.; M.S.	+ +	?	?	+	?	?	+	M.	+		+
W.	28	A.R.; M.S.	+ +	?	?	—	4	—	—	D.	+		+
P.	35	A.R.; M.S.	+ +	?	?	—	3	—	—	S.	+ + +	Died	+ + +
C.	39	A.R.; M.S.	+ +	?	?	—	?	2	—	P.D.	+		+
L.	39	A.R.; M.R.	+	R.F. 25	6	—	10	1	—	S.	—	Fair; E.T. 9 = 2·5	—
1541	24	Fib.‡ M.S. and M.R.	+ + +	R.F. 19	19	+	2	—	+	S.	+	Aur. fibrill.; E.T. mod.	+ + +
366	29	Fib. M.S. and M.R.	+ +	—	12	+	1	2	—	S.	—	Moderate.	+
4301	29	Fib. M.S. and M.R.	+ +	R.F. 12	3	—	?	?	+	S.	+ + +	Aur. fibrill.	—
137	34	Fib. M.S. and M.R.	+ +	—	—	—	2	—	+	D.	+ + +	Died 1923	+ + +
Tr.	24	Fib. M.S.	+ +	?	?	—	1	—	—	S.	+ + +		+
Av.	37	Fib. M.S.	+ +	R.F. 16	4	—	8	—	—	S.	+ + +		+
Ed.	41	Fib. M.S.	+ +	?	?	+	?	?	+	M.	+ + +		+

* S., satisfactory; M., miscarriage; P., premature; D., died or still-born.

† E.T. 9 = 2·5 denotes with an exercise tolerance test of 9 steps a minute for three minutes the pulse ratio was 2·5.

‡ Auricular fibrillation.

with the shortest history it averaged 13 years; in the next eight, 16; in the next eight, 22, and in the eight with the longest history 30 years.

The duration of symptoms was also very variable and averaged 6½ years, so that there had generally been a long interval between the original infection and the first symptoms which were sufficiently striking to be recalled. It must be remembered that several of the patients did not complain of any symptoms. The exact periods in those who did were 1–2 years in 14 patients; 3–4 years in 12; 5–6 years in 11; 7–8 years in 5; 9–10 years in 2; 11–12 years in 2; 13–14 years in 1; 15 years or more in 7.

From these figures it seems unlikely that the patients are the same group as those generally seen in the medical wards from 15–25 years old with valvular disease. Probably their early symptoms are sufficiently severe to make marriage, or at any rate pregnancy, less likely.

This is also shown by the number of children whom many of these patients had borne already. Only 13 were primiparæ, 19 had one child already, 15 two, 8 three, 4 four, 4 five, 4 six and 12 more than this. But the number of miscarriages was one to every six normal births, much more than in the average population.

Conclusions

The results given in Tables I–IV amply confirm Hunt's conclusions, which can fortunately be given almost in his own words.

1. Provided the heart is not enlarged, patients with mitral disease stand pregnancy well and there is not much extra risk.

2. If the heart is enlarged, the risk is increased, and it does not make much difference whether the valvular lesion is aortic regurgitation or mitral stenosis. The amount of extra risk depends on the degree of enlargement and the treatment which can be adopted during pregnancy.

3. In auricular fibrillation the results are so disastrous that pregnancy should be prohibited.

A CASE OF ANNULAR MUSCULAR HYPERTROPHY OF THE ŒSOPHAGUS

(ACHALASIA OF THE CARDIA WITHOUT ŒSOPHAGEAL DILATATION)

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THE specimen to be described came from R.C., *æt.* 67, a watchman, admitted under Mr. W. H. Ogilvie on December 17, 1925. He gave a three months' history of a swelling on the right side of the tongue, with pain radiating up to the right ear. An operation for removal of the growth was performed on December 21, when the anterior half of the tongue was removed and the anterior triangle of the neck cleared of glands. On December 22 the patient's temperature rose and he died on December 23. An autopsy was performed by Prof. Stokes on December 24, sixteen hours after death. The following is a summary of the report :

A well-built man showing only slight signs of wasting. The operation site was free from obvious infection. No carcinomatous glands were found in the neck. Both lungs showed chronic pleurisy and were adherent to the chest wall. The right base was irregularly consolidated and showed a greenish-brown surface on section; areas of the lung were breaking down and emitted a foul odour. The left lung showed the same condition to a less degree. The heart was atrophied; there was coronary arteriosclerosis. The aorta showed advanced arteriosclerosis with ulceration and adherent thrombi.

The œsophagus (Pl. I. fig. 1) presented an area of hypertrophy beginning opposite the bifurcation of the trachea, 4 cm. below the cricoid cartilage, extending downwards for about 9 cm., the change from normal thickness to hypertrophy being gradual at each end, and ending 4 cm. from the cardiac orifice of the stomach. The last 4 cm., however, were slightly thicker than normal, although this was not apparent until measurements had been made (Table I).

TABLE I.

	Thickness of wall in specimen.	Thickness of normal wall.	Diameter of lumen in specimen.
Just below cricoid cartilage . .	0·2 cm.	0·13 cm.	4·0 cm.
In middle of hypertrophied area .	0·8 ,,	0·25 ,,	1·8 ,,
Just above cardia	0·45 ,,	0·3 ,,	2·4 ,,

The hypertrophy was in the muscular coat and was entirely confined to the inner circular fibres. On the anterior aspect of the mucous membrane there were two small depressions suggesting early diverticula, but they were clearly caused by the muscular constriction throwing the mucous membrane into folds. There was slight dilatation of the œsophageal lumen above the hypertrophied area, but there was no dilatation above the cardia (Table I). The muscular wall in the lower segment was soft and flaccid in contrast to the area above the hypertrophy. The cardiac orifice was normal and no evidence of stricture or obstruction could be found. There were no mediastinal glands which might have pressed on the œsophagus. Careful search failed to reveal any macroscopic cause of obstruction. The stomach was normal, but the pyloric aperture was noted as "tight." No other abnormalities were found.

It is important to note that no history of difficulty in swallowing could be obtained from the widow.

Microscopic Examination of the Œsophagus

The tissues were fixed in 10 per cent. neutral formalin in normal salt solution. Blocks were cut from four areas: the extreme lower end, the lower end of the hypertrophied area, the middle of the hypertrophy, and above the hypertrophy. These blocks were cut in serial section except the one above the hypertrophy. The sections were stained with hæmatoxylin and eosin, hæmatoxylin and Van Gieson. Frozen sections were cut and stained for Nissl granules with negative results so far as the demonstration of the granules was concerned, possibly owing to post-mortem autolysis and formalin fixation. The lesions found diminish in intensity from below upwards; they will therefore be described in this order.

In the sections of the block at the lower end the most striking change was that involving Auerbach's plexus, lying between the circular and longitudinal coats. The ganglia were considerably larger than normal, as will be seen by comparing Pl. II. fig. 2, a drawing from a ganglion in the lower segment, with Pl. III. fig. 3, a microphotograph of a ganglion at the same level in a normal œsophagus, an average example taken from one of six œsophagi examined as controls. Both illustrations have the same magnification.

In the second place, all the ganglia examined below the hypertrophied area showed some degree of inflammatory change. The evidence of inflammation varied from what appeared to be almost an acute process to one in which there

was fibrosis with little or no cell infiltration. In the more acutely inflamed ganglia the vessels were dilated and engorged, there was cell infiltration, in many ganglia best seen around the vessels, and frequently eosinophile cells were found. The ganglion cells themselves suggested advanced degeneration, but on account of the possibility of post-mortem autolysis it is difficult to be certain of this change. In several instances wandering cells appeared to be invading the degenerate ganglion cells (Pl. III. fig. 4, and Pl. IV. fig. 5). In other ganglia there was considerable fibrosis, relative poverty in ganglion cells and evidence of their disintegration (Pl. IV. fig. 6).

The inflammatory process was not confined to the ganglia, but was also evident along the nerves running from the plexus to the muscles, cell infiltration along the small nerves frequently being seen (Pl. V. fig. 7).

A third change was noted in the nerves—an increase in the cellularity of the nerve sheath. Pl. V. fig. 8 shows such a nerve coming off at the lower pole of a ganglion, in which the proliferation of the sheath, apart from any inflammatory reaction, is very apparent.

With polychromatic stains, mast cells were seen in a number of ganglia, but the majority of the invading cells were lymphocytes with a small number of eosinophiles. No bacteria were demonstrated. There was active hyperæmia, especially well seen around the nerves and ganglia, and around the smaller vessels wandering cells appeared to be numerous. There was a general fibrosis of all the tissues, the sheath of the plexus and the circular coat showing much increase in fibrous tissue. The fibrous supporting stroma was also much increased (Pl. VI. fig. 9).

The undamaged muscle fibres seemed to be larger than usual, and the muscle nuclei appeared to be not only more numerous, but also larger than normal. In places the inflammation involved the muscles, so that we have a complicated picture of muscle cells, in some places surrounded by dense fibrosis and in others showing cell infiltration with round cells and eosinophile leucocytes. Summarising, all the tissues show the early and late changes associated with a subacute or chronic inflammatory process, the changes being most evident in the ganglia.

In the second and third series of sections inflammatory changes were difficult to find, both in the plexus and in the other tissues. The ganglia as a whole were smaller and only two out of a long series gave real evidence of inflammation, which was in both instances acute in type. The muscle was greatly hypertrophied and exhibited no signs of fibrosis or cell infiltration; there was no vascular congestion. Here then we

have very little change, but that of an acute nature, perhaps an indication that the changes found in the lower segment were spreading upwards.

The fourth series may be briefly dismissed. There were no signs of inflammation anywhere, and the tissues were normal, very different from the first series described (Pl. VI. fig. 10).

Discussion of the Specimen

A necessarily superficial search of the literature has revealed four cases similar to the one here recorded. These were described by Newton Pitt,[1] Rolleston,[2] Elliesen,[3] and Ehlers.[4] The case described by Rolleston is so similar to the one here discussed that it may be briefly summarised.

Male, *æt.* 59, gave no history of difficulty in swallowing. The condition was found accidentally at autopsy. From three inches below the cricoid, progressing to the cardia, there was hypertrophy affecting the circular muscular coat. The hypertrophy did not tend to increase as the stomach was approached. The cardia was normal in size and no mechanical obstruction could be observed. The stomach was large and the pyloric orifice small. On microscopic examination no inflammation or fibrosis was discovered. This specimen differs from the one under discussion in two particulars: first, that the hypertrophy extended down to the cardia, and second, that no microscopic lesions were found.

When the specimen under discussion was first seen at autopsy, the writer suggested that it might represent a well-compensated achalasia of the œsophagus. It was therefore interesting to find on reading Rolleston's [2] paper that he had made the same suggestion with regard to his specimen. The same explanation has also been suggested by Shattock,[5] who says: "In connection with muscular hypertrophy of the œsophagus without dilatation, it is enough to point out that it may represent a completely compensated achalasia or even cardiospasm, a possibility conceived by Dr. Brown Kelly.[6] This could only be established by finding such hypertrophy unassociated with aortic aneurysm, enlargement of the heart, or other extrinsic mechanical obstruction."

An attempt will now be made to picture the mechanism which gave rise to the localised hypertrophy and which, it is suggested, leads in its later stages to cases recognised clinically as achalasia.

It is necessary in the first place that there should exist some lesion which will interfere with the nervous control of the œsophageal sphincter. Among the lesions which have

been associated with achalasia the following have the best claim to ætiological significance.

1. Cannon [7] has shown that physiologically, when free hydrochloric acid is present in the stomach, the cardia does not open. Such a condition will not cause achalasia, but is of assistance in understanding how achalasia may arise reflexly in association with gastric lesions, including ulcer and carcinoma.

2. Howarth [8] quotes a case in which there was a small tumour in the wall of the subdiaphragmatic œsophagus which, presumably on account of local irritation, gave rise to achalasia. Similar cases have been recorded by other authors.

3. Vagal lesions have been found in this condition, and an example of atrophy of the nerve has been described by Kraus,[9] who emphasised the importance of determining the integrity of the vagus in all cases. In other instances the nervous lesion has been central, and in still others involvement of the nerve by enlarged glands and by tumours has been described. It is interesting here to notice that Kronecker and Meltzer [10] working in 1883 produced in rabbits a condition essentially similar to clinical achalasia by division of the vagus.

4. Achalasia has followed infection and toxæmias, acute and chronic, especially such as give rise to nerve lesions in other parts of the body; for example, diphtheria, syphilis and Bright's disease. It is probable that in these conditions the achalasia has followed a toxic neuritis. Kraus [9] has recorded a case following whooping cough.

5. Finally, it is suggested that achalasia may be caused by inflammatory changes in Auerbach's plexus. In this connection it is interesting to note that Keith [11] has shown that the plexus at the lower end of the œsophagus contains a large admixture of nodal tissue similar to that present in the auriculo-ventricular bundle of the heart. We might then consider the changes in the plexus in the case described as comparable to that found in the heart in cases of Stokes-Adams disease. It should be noted that Hurst [12] had already foreseen the changes found in the specimen, for he says: "It seems likely that the majority of cases of achalasia of the cardia are caused by progressive organic disease involving Auerbach's plexus."

If then any one of these lesions has occurred, it is a fair inference that the nervous control will be so damaged that normal reflex action will not take place. In the case under discussion the outstanding lesions were in the plexus and the most advanced changes were below the region of hypertrophy. One may believe that in this area peristalsis, depending as it

does on normal reflex action, did not take a normal course and that the bolus having reached this point was held up owing to failure of relaxation. The food was churned up and down above the obstruction and very gradually passed through into the stomach. If the process as described is carried on long enough and with sufficient vigour, the next step would be hypertrophy of the œsophagus above the unrelaxing segment, the normal response to obstruction.

Assuming the above argument, we now have a compensation which may be sufficient to overcome faulty relaxation, as it presumably was in this case, no symptoms having been present. On the other hand, the compensation may just fall short and the hypertrophy will gradually be obscured by dilatation, symptoms will occur and the case become one of clinical achalasia.

It is important to realise that compensation and adaptation must often be very efficient. This is indicated by the well-recognised clinical fact that patients, when they first complain of the symptoms, are often found with enormous dilatation of the œsophagus, easily demonstrated by x-rays and by the great quantity of food which they regurgitate, half a pint or more. Thus, finally, in most chronic cases, following the rule of all obstructions in tubular organs, the compensatory hypertrophy gradually gives place to dilatation.

The question of intermissions here arises, as some patients have long periods of freedom, years in some cases. One must believe that in these cases the lesion set up by the infection or any other cause has healed, in the first instance, leaving so little organic change that compensation has been all-sufficient, the recurrence of the symptoms coinciding with the return of the causal agent.

In most cases of achalasia the hypertrophy and dilatation extend down nearer to the cardia; an objection might then be raised to the above theory of the significance of this specimen, that since the hypertrophy proper is so far above the cardia (*i.e.* 4 cm.) it cannot be the forerunner of achalasia. This objection is justifiable if the cardiac sphincter is regarded as a narrow band between the œsophagus and the stomach. Hurst,[13] however, has shown that the cardiac sphincter varies in length up to three or more centimetres. It is therefore probable that in this case the sphincter was even longer than usual and extended four centimetres above the actual cardiac orifice.

Sir Arthur Keith, who kindly examined the sections, told the writer that the large size of the ganglia found in the present

specimen was also a characteristic of the ganglia found near the pelvi-rectal sphincter in Hirschsprung's disease. This condition has been shown by Hurst [12] to be due to achalasia of the pelvi-rectal junction.*

Another point to be considered is the eosinophile infiltration of the tissues. This might suggest that the primary cause of the lesions found was syphilitic, and although this must remain an unprovable suggestion, one should note that the patient had a carcinoma of the tongue and recall the common antecedent of the condition. As has been mentioned above, syphilis has been recorded as a cause of achalasia.

An interesting feature is to be found both in Rolleston's case and in the one under discussion—the narrowing of the pylorus. There is no explanation, but the coincidence suggests a sphincteric disturbance in this region as well as at the cardia. Unfortunately, the pylorus was not preserved for microscopic examination. The association of disturbance of the cardia with disturbance of the pylorus would seem to be frequent. Thus there are two specimens of achalasia in the Gordon Museum, and in both large dilated stomachs were present. Again, Still [14] points out that in the hypertrophic pyloric stenosis of infants, which is caused, as Cameron has shown, by achalasia of the pylorus, there is frequently a narrowing of the cardiac orifice.

In conclusion it seems desirable to emphasise that, although a previously undescribed lesion involving Auerbach's plexus has been recorded in a condition believed to be a fully compensated achalasia, it is not suggested that this is a constant cause of the condition. Many other undoubted causes have been discussed, and there are other cases recorded for which no cause can be found and in which examination has failed to reveal any ganglionic lesions microscopically. In fact no lesion of the plexus has been hitherto recorded, although it is clear that such changes have occasionally been sought for.

My thanks are due to Mr. W. H. Ogilvie for permission to record this case, to Mr. R. Davies-Colley for permission to make use of tissues from the Gordon Museum, to Dr. G. W. Nicholson for his kindness in making the drawing, and to Sir Arthur Keith for his kindness in going over the sections with me, and for his numerous valuable suggestions.

* It may be mentioned that in two cases of Hirschsprung's disease which the writer examined this enlargement of the ganglia was not observed.

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PLATE I

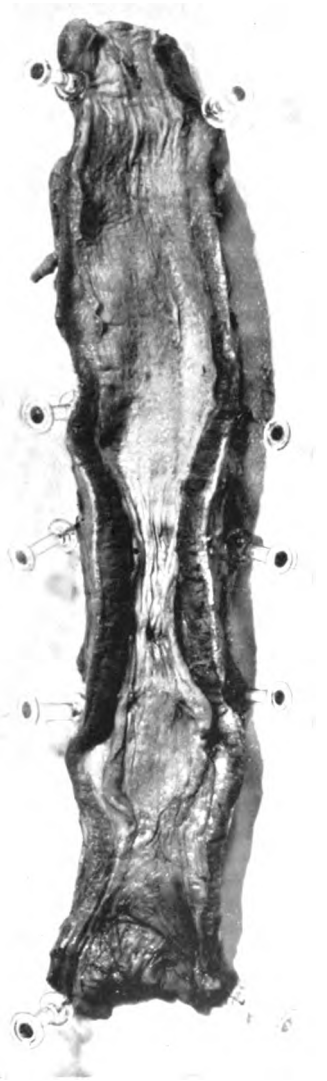

FIG. 1.

Œsophagus showing muscular hypertrophy commencing 4 cm. from the cardia. $\frac{2}{3}$rds natural size.

PLATE II

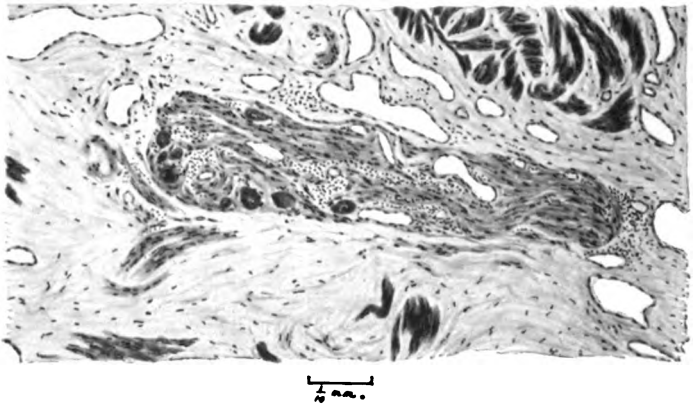

FIG. 2.

Drawing of inflamed ganglion from lower end of œsophagus. Cell infiltration in the ganglion, fibrosis of surrounding tissue. × 100.

PLATE III

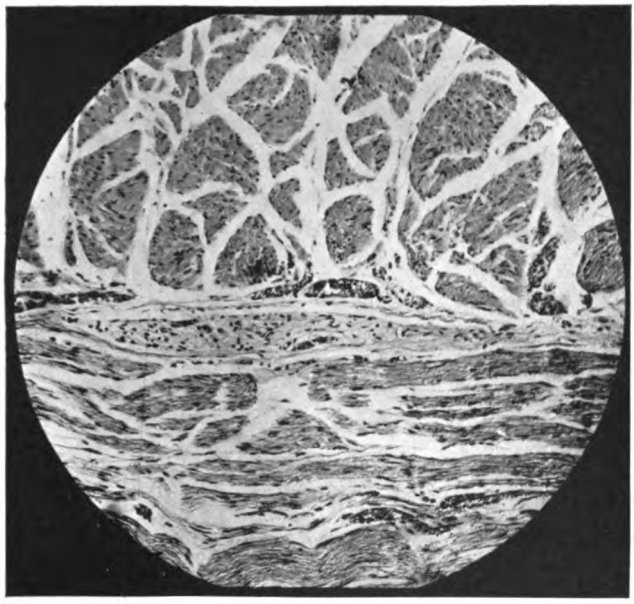

FIG. 3.
Microphotograph of a normal ganglion. × 100.

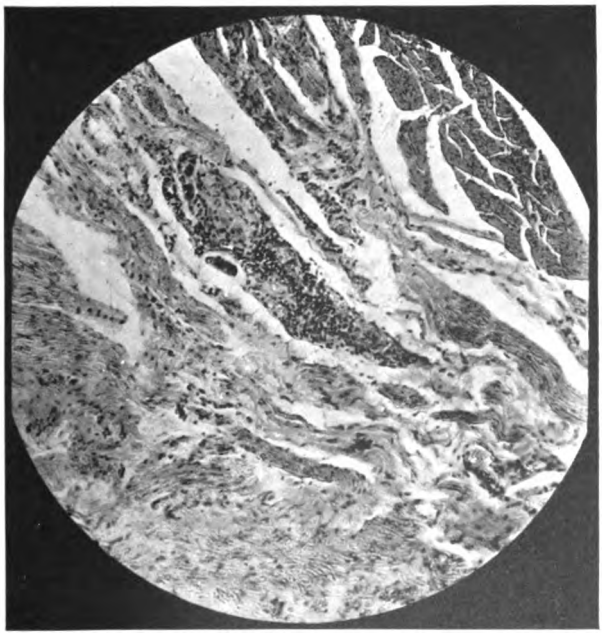

FIG. 4.
Microphotograph of ganglion showing cell infiltration and degeneration of ganglion cells.

PLATE IV

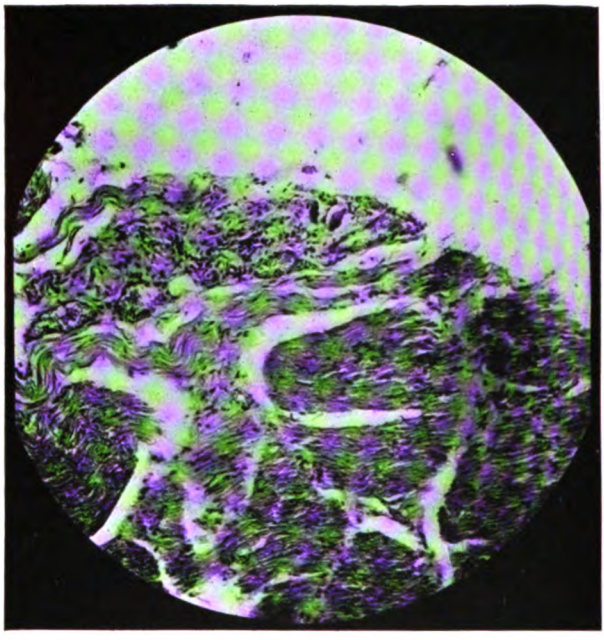

FIG. 5.

Microphotograph of ganglion, showing subacute inflammatory changes. × 100.

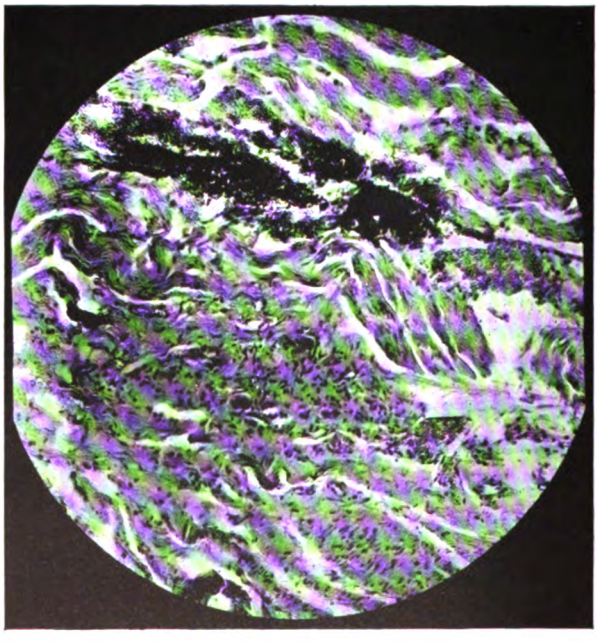

FIG. 6.

Microphotograph showing fibrosis of ganglion and surrounding tissue. Relative poverty and degeneration of ganglion cells. × 100.

PLATE V

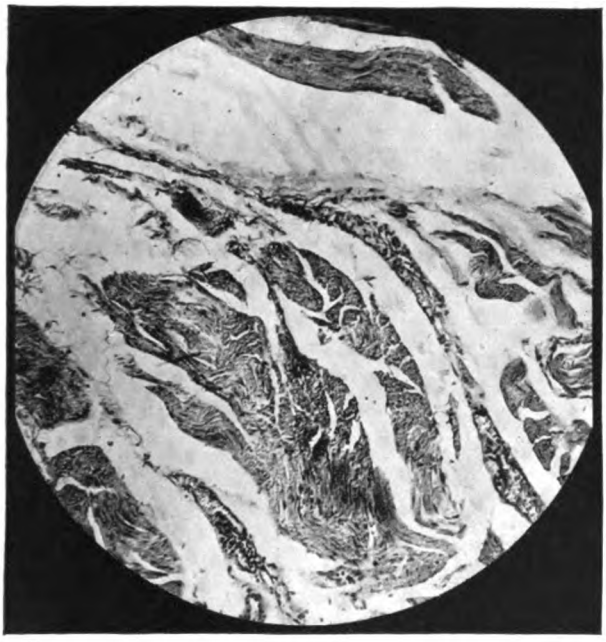

FIG. 7.
Cell infiltration and proliferation of sheath in nerve after leaving ganglion. × 100.

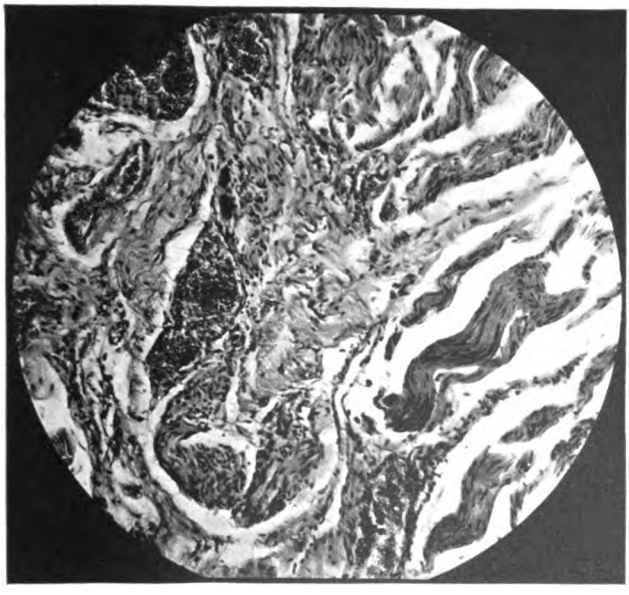

FIG. 8.
Nerve leaving lower pole of ganglion showing proliferation of sheath. × 100.

PLATE VI

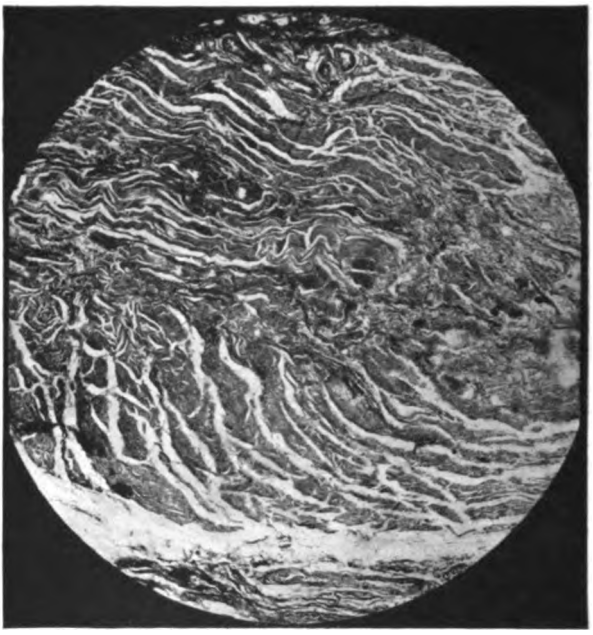

FIG. 9.
Fibrosis and cell infiltration of the muscular coat. × 50.

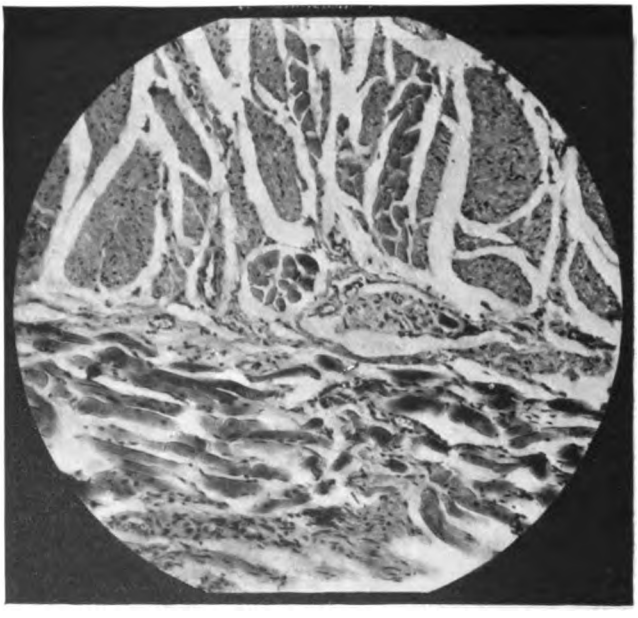

FIG. 10.
Normal ganglion from the upper segment of the œsophagus. × 100.

A CASE OF DYSPHAGIA DUE TO POSTERIOR PHARYNGO-ŒSOPHAGEAL POUCH

By W. E. TANNER, M.S., Assistant Surgeon to the Prince of Wales's General Hospital and Surgeon to the Evelina Hospital for Children.

DR. A. F. HURST'S account of a case of dysphagia due to an anterior pharyngo-œsophageal pouch in the July volume of the *Reports* leads me to publish the notes of the following case.

S. K., male, age 53, was seen in May 1925 for difficulty in swallowing. In 1915 he noticed a peculiar sensation in his throat which made him cough. At the same time he found that he was unable to swallow solid food. After taking a certain amount, he felt the food sticking in his throat, and one hour later the food was regurgitated unchanged. He said that the condition was no worse than it was ten years ago. He enjoys drinking, but cannot take meat; he says, moreover, that he can drink neat whisky like water. He is a heavy smoker, suffers from bronchitis, and has been losing weight lately. There is no history of venereal disease.

On admission he was thin and wasted. There was no affection of the voice and no mass palpable in the neck. The pupils were equal, and nothing abnormal was detected in the heart or abdomen.

The heart was not displaced. The movement of the right side of the chest was diminished, and the vocal fremitus and percussion note were impaired at the right apex in front and in the upper half of the left lung behind. Expiration was prolonged everywhere; bronchial breathing was heard at both apices, but harsher on the right side. Coarse crepitations occurred on coughing at the right apex in front and at the apex of the left lower lobe behind. There was marked increase of vocal resonance at the right apex.

The sputum contained large numbers of tubercle bacilli.

X-ray examination showed a diverticulum at the commencement of the œsophagus and marked peri-bronchial mottling. The radiogram (Fig. 1) shows the lower part of the pouch filled with barium and the narrower upper part extending upwards and to the left to the level of the body of the sixth cervical vertebra.

The radiographer, Dr. S. C. Shanks, reported, "Almost complete obstruction to the opaque bolus (a thick cream) just above the level of the aortic arch." This shows that the dysphagia was the result of compression of the œsophagus by the lower part of the distended pouch in the confined space of the

upper thoracic inlet—between the bodies of the third and fourth dorsal vertebræ posteriorly and the manubrium sterni anteriorly.

Examination with the œsophagoscope showed the transverse slit-like opening of the pouch on the posterior and left side of the œsophagus opposite the lower border of the cricoid cartilage.

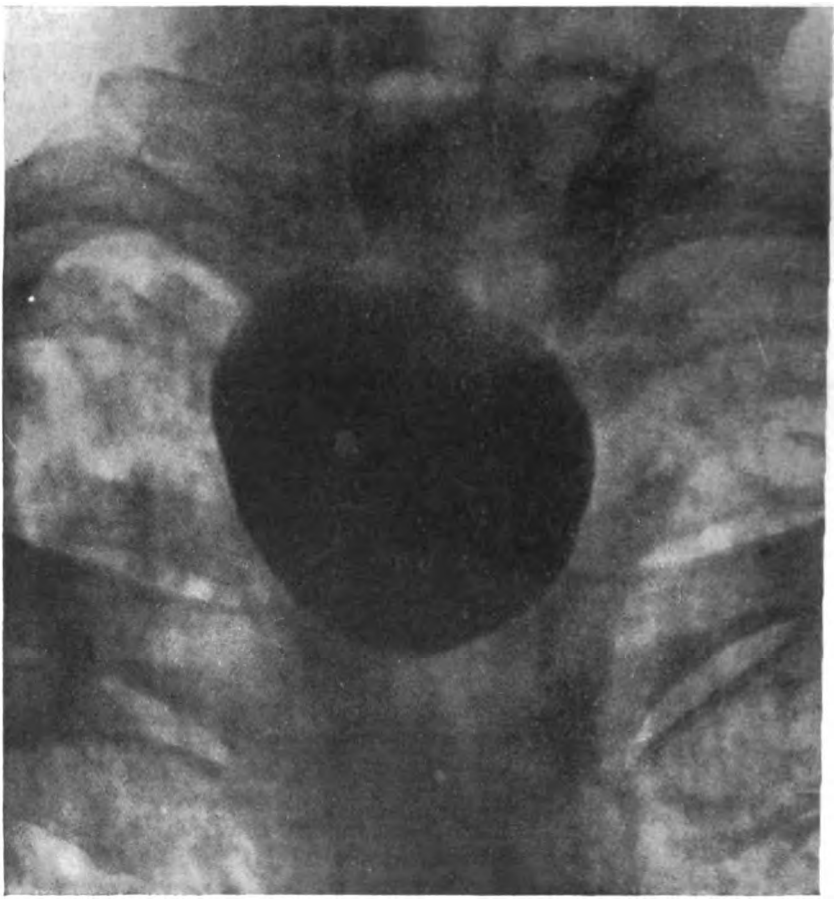

FIG. 1.

Radiogram of œsophageal pouch (Dr. S. C. Shanks).

On pressure mucus poured out of the opening. There was no narrowing of the œsophagus.

Operation.—Under chloroform anæsthesia an incision was made just internal and parallel to the anterior border of the lower part of the left sterno-mastoid. The sterno-mastoid and the carotid vessels were pushed outwards; the depressor muscles of the larynx, the thyroid gland and the trachea were pushed inwards, exposing the œsophagus. The diverticulum was then pulled out of the wound. The sac was not attached to

surrounding structures and was not inflamed. In view of this and of the presence of phthisis, it was decided to excise the sac in a one-stage instead of the more usual two-stage operation. The neck of the sac, one inch in diameter, was crushed and then closed with a purse-string suture. The sac was excised and the defect in the muscles closed with two layers of interrupted catgut sutures placed transversely. The wound was then closed, a rubber glove drain being left in the lower angle. The glove drain was removed after forty-eight hours. The patient was fed *per rectum* for four days and was then allowed to take fluids by mouth. The wound healed *per primam*.

The patient can now swallow fluids and solids quite easily and radiographic examination shows no obstruction. Despite signs of active phthisis he is gaining weight and his health has improved.

Comments

1. The opening of the pouch was merely a transverse slit except during deglutition, when the upward pull of the pharyngeal muscles and the downward pull of the œsophagus opened it so that food was forced into the pouch.

2. The following points are of interest :—

(*a*) The association of phthisis with a pressure diverticulum.

(*b*) The absence of stenosis of the œsophagus.

(*c*) The obstruction in the œsophagus was most marked just above the aortic arch and was due to the filling of the lower part of the pouch.

(*d*) The absence of fœtor of the breath because the man's addiction to neat whisky kept the pouch clean.

(*e*) The success of a one-stage operation. In this case it would have been possible to have avoided the risk of mediastinitis altogether by turning the pouch inside out within the œsophagus, suturing the muscles, closing the neck wound and then removing the pouch from within the œsophagus.

THE ASSOCIATION OF CHRONIC DUODENAL ILEUS WITH GASTRIC AND DUODENAL ULCER

I. GASTRIC AND DUODENAL ULCER ASSOCIATED WITH CHRONIC DUODENAL ILEUS; RADIOLOGICAL DIAGNOSIS; PARTIAL GASTRECTOMY

By A. F. HURST, M.D., Physician to Guy's Hospital, and P. J. BRIGGS, M.A., Radiologist to New Lodge Clinic.

In the *Reports* for October 1922, one of us (A. F. H.) discussed the etiology and symptoms of chronic duodenal ileus, and described two cases in which the diagnosis had been made with the x-rays, the first in 1914 and the second in 1921. He showed how the condition would be likely to predispose under certain circumstances to the development of duodenal ulcer and possibly also gastric ulcer, and referred to the occurrence of a duodenal ulcer in three and a gastric ulcer in one of eleven cases of chronic duodenal ileus recorded by Wilkie in 1921. The following case is of special interest, as both a gastric ulcer and a duodenal ulcer were found in a young man with chronic duodenal ileus, all three conditions being diagnosed with the x-rays and confirmed at operation.

Mr. E., aged 21, was admitted to New Lodge Clinic on December 30, 1925. He had had an acute attack of pain with vomiting in the middle of the night six years before. From this time he began to have pain punctually an hour and a half after meals, which was relieved by the next meal or by taking an intermediate feed. It woke him at night, but was again relieved by a glass of milk. His appendix was removed in 1920, but this only gave him incomplete and temporary relief. During the last five months he had had a severe ache between the scapulæ at the same time as his epigastric pain. Recently he had only been comfortable when in bed on a very light diet.

An x-ray examination showed that in addition to the duodenal ulcer, which was naturally suspected on account of the symptoms, a gastric ulcer of considerable size was present on the lesser curvature (Fig. 1). The deformity produced by each ulcer was quite characteristic, and the two craters were the seat of definite localised tenderness. In addition to the ulceration, a condition of chronic duodenal ileus was found. The whole of the duodenum proximal to the point where it is crossed by the root of the mesentery was considerably dilated, and constant

vigorous backward and forward movements were observed in it. Neither ulcer directly involved the pylorus and neither of them caused any reflex disturbance in its activity, as the stomach was found to be completely empty in less than four hours after the opaque meal. The duodenal obstruction was also incomplete, as there was no residue present in it after the stomach had completely evacuated its own contents. It was found that the dilated duodenum could be immediately emptied

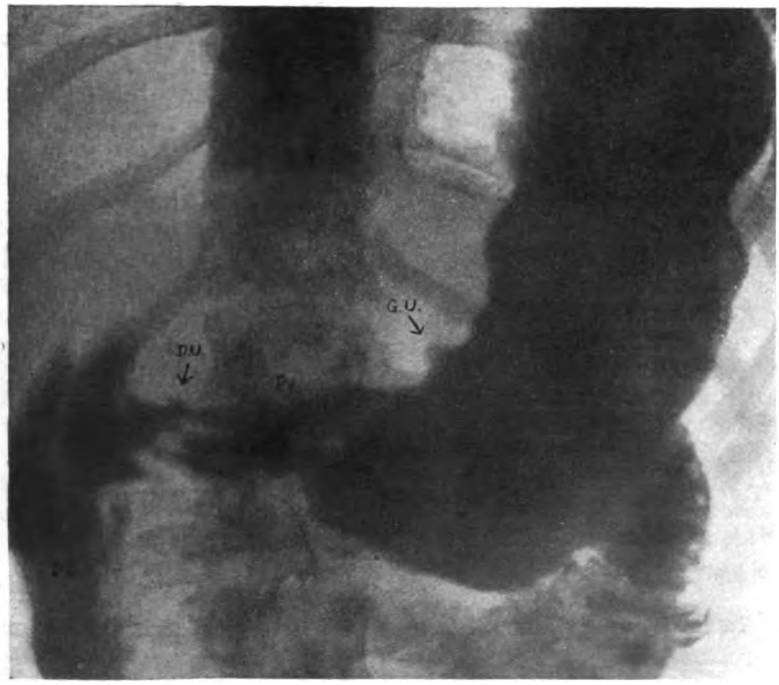

FIG. 1.

Radiogram of stomach and duodenum, showing crater of gastric ulcer (G.U.), crater of duodenal ulcer (D.U.), and deformed duodenal bulb. Py, pylorus; D.D., descending part of dilated duodenum.

if the patient got into the knee-elbow position, thereby removing the drag upon the root of the mesentery.

A fractional test-meal showed a mild degree of hyperchlorhydria and confirmed the absence of any pyloric obstruction, as the stomach was completely empty in one and three-quarter hours. The stools contained traces of blood, as shown by chemical tests and by giving a hæmatoporphyrin spectrum, so that there was no doubt about the activity of the ulcers. Though the urine was normal, the presence of duodenal obstruction made it desirable to test the renal efficiency, as obstruction frequently leads to a certain degree of renal insufficiency, which makes it a matter of considerable danger to give the usual

strenuous alkaline treatment for an ulcer; in such cases severe symptoms of alkalæmia, resembling those of uræmia, may result.[1] The blood urea was found to be 82 mgr. per 100 c.c., compared with the normal of 30 mgr., so definite renal insufficiency was present. For this reason the patient was given tribasic calcium phosphate and tribasic magnesium phosphate instead of the usual alkalis, as, although these act as alkalis in neutralising the acid of the stomach, they do not increase the alkalinity of the blood and can therefore be given in cases of pyloric or duodenal obstruction without danger. The renal insufficiency actually diminished during the treatment, the blood urea falling to 60 mgr. per 100 c.c. some days later.

In spite of very careful treatment by rest in bed, diet, alkalis, atropine and olive oil, when readmitted on February 20, 1926, it was found that the craters of both ulcers were still present and there was still occult blood in the stools. The duodenal ileus was as well marked as ever.

An operation was therefore advised. The following is Mr. R. P. Rowlands' report: "The diagnosis was confirmed in every particular. Partial gastrectomy was performed on March 1, and the jejunum anastomosed to the cut end of the cardiac remainder of the stomach after the Polya-Balfour-Moynihan method. The part removed comprised the pyloric half of the stomach and the first part of the duodenum. The crater of the gastric ulcer was the size of a sixpence; the duodenal ulcer was almost healed and was on the anterior wall of the duodenum close to the pylorus. The duodenal ileus was caused by a tightness of the root of the mesentery with no evidence of active disease or glandular enlargement."

The patient writes on March 21: "I came out of Guy's yesterday, feeling extremely well and quite different to my previous self."

II. GASTRIC ULCER ASSOCIATED WITH CHRONIC DUODENAL ILEUS; PARTIAL GASTRECTOMY

By R. P. ROWLANDS, M.S., Surgeon to Guy's Hospital.

Henry H., aged 29, first noticed pain in the upper abdomen four months ago. It always started in the epigastric region, and often spread into the thorax and up to the shoulder. It was of a dull, aching or burning character. It came on immediately after taking food and was attended by flatulence and occasionally by vomiting. He dieted himself, leaving off meat, with some relief of pain.

On admission to Guy's Hospital under Mr. Rowlands on September 21, 1925, he looked very ill and was rigid and tender in the left epigastric angle. A very acute attack of pain doubled him up on the day after his admission.

The x-rays showed retention of a flake of barium on the

posterior surface of the stomach, high up towards the cardia, indicative of ulcer. The fæces gave a positive guaiac test, and a faint hæmatoporphyrin spectrum. There was no hyperchlorhydria. On account of the failure of medical treatment, the large size of the ulcer and the intolerable pain an operation seemed to be imperative.

A long left paramedian incision in the epigastric angle on September 24 showed a large gastric ulcer high up on the lesser curvature. The appendix was adherent and inflamed and was removed. The omentum was also adherent in the pelvis near the appendix. There was marked duodenal ileus; partial gastrectomy appeared, therefore, to be the best treatment and was carried out. The ulcer was very large and adherent to the pancreas, which the crater had penetrated, so that a slice of the front wall of the pancreas had to be removed with the ulcer. About half the stomach was removed and the anastomosis made after the Polya-Balfour-Moynihan method.

Microscopic examination showed a simple peptic ulcer; the glands showed chronic inflammation.

Although the wound gave way a week later during a fit of coughing, the patient did well, and was able to leave the hospital a month after the operation. He was seen on March 16, 1926, looking well. He had put on much weight and had not been sick since the operation, and had had no pain since leaving the hospital.

Partial gastrectomy seemed to meet the demands of this case better than any other operation or combination of operations such as excision of the ulcer, gastro-jejunostomy and duodeno-jejunostomy. In some cases of complete or severe duodenal ileus, duodeno-jejunostomy will have to be added, but this addition did not seem or prove necessary in my two cases.

III. TWO CASES OF DUODENAL ULCER ASSOCIATED WITH CHRONIC DUODENAL ILEUS

By J. GAYMER JONES, M.S., Surgical Registrar, Guy's Hospital.

Case 1.—William H., aged 19, was admitted on December 30, 1924, for acute abdominal pain. For two and a half years he had suffered from attacks of pain in the abdomen which had necessitated his seeking medical treatment almost every month. The pains were situated just above the umbilicus. On Christmas Eve, 1924, he had an attack of abdominal discomfort associated with regurgitation of watery fluid into his mouth. This passed off the next day, but on December 29, at five o'clock in the evening, he had acute pain in the usual position and sent for his doctor. The following morning, as the pain persisted, he was sent to Guy's Hospital, and was admitted as an abdominal emergency.

At operation the appendix was found to be inflamed and was removed, but it was felt that the amount of inflammation present

did not fully account for his symptoms. The stomach and duodenum were therefore examined, and a small perforation found in the first part of the latter, but the most striking feature in the abdomen was the great distension of the duodenum, which extended up to, but not beyond, the superior mesenteric vessels. The perforation was sewn up, and, as it was decided that the operation ought not to be prolonged more than was absolutely necessary, the abdomen was closed.

On the twelfth day after operation the patient complained of abdominal pains and vomiting. This was so persistent that a Ryle's tube was passed, and was connected by way of a Woulfe's bottle to a Sprengel's suction pump (*vide* Appendix). For three days this treatment was carried out, as it was thought that the condition was due to an acute aggravation of chronic duodenal ileus, but it became evident that something further had to be done. The abdomen was opened again, and a loop of jejunum was found to be obstructed by a band of omentum. This was relieved and the patient made a rapid recovery.

Before going out he was x-rayed. The following is Mr. Magnus Redding's report: "Stomach shows slight dilatation. Mobility good and meal leaves freely. No deformity of stomach. Very little deformity of first part of duodenum to indicate the site of the perforation. No pyloric stenosis. Definite duodenal ileus with dilatation of the second and proximal part of third portions of the duodenum. *6th hour.*—Stomach empty; meal occupies small gut, cæcum, ascending and transverse colons."

When seen on March 29, 1926, he said that he had had no return of pain or discomfort of any kind and was feeling very well.

The points of interest in this case are these:

(1) The boy started suffering from attacks of abdominal pain between the ages of sixteen and seventeen, *i.e.* long before the symptoms of duodenal ulcer usually occur. It seems fair to assume that these attacks were due to duodenal ileus, which preceded the ulcer.

(2) On further questioning it was found that a brother had also been operated upon at the age of nineteen for a perforation of the "stomach." It is interesting too that he also developed symptoms of obstruction ten days after the first operation and died. Whether this obstruction was due to an acute aggravation of chronic duodenal ileus, or to some such cause as was found in the above case one cannot say.

Case 2.—Thomas R., aged 42, stoker, attended the Out-Patient department in January 1924 for an attack of "gastritis." There was a history of previous indigestion. An x-ray examination revealed nothing abnormal. In October 1924 he attended Out-Patients again and gave a history of pain in the right hypochondrium coming on three and a half hours after meals,

and radiating to the left hypochondrium. He also complained of flatulence and nausea. His stools were dark and fluid and he thought that he had lost weight. In April 1925 he attended Out-Patients for another recurrence and was x-rayed again. The report stated: "Stomach orthotonic. Mobility somewhat exaggerated and meal leaves rapidly. There is a small deformity of first part of duodenum indicative of ulceration. No pyloric stenosis. No gastric delay." The pain came on three and a half hours after meals and was relieved by food or water. It did not wake him at night.

The patient was admitted on May 15, 1925, to the medical wards under Dr. J. A. Ryle. There was some tenderness in the right hypochondriac and lumbar regions. Test-meal showed hyperchlorhydria and no delay. Frequent tests of the fæces for blood showed small remnants to be present in the earlier specimens, but the reports on the last three were "Practically no blood," "No blood," and "Practically no blood." A further x-ray examination was performed on May 20; the report states: "Stomach normal in position, shape and size; peristalsis active; greater curvature 1″ below iliac crest in erect position; no ulceration seen. Duodenal cap appears to be well formed and is only very slightly tender. Barium is leaving freely. *6th hour.*—Barium in terminal ileum, cæcum, and ascending colon; appendix not seen, but tenderness over ileo-cæcal junction. *24 hours.*—Barium in pelvic colon and rectum."

The patient was given an ulcer diet and was free from pain by the fourth week. He was discharged on June 26, 1925. After leaving hospital he remained free from symptoms for a month, but these then returned, and he attended Out-Patients at intervals. He was eventually transferred to the surgical side and was admitted on January 4, 1926. A laparotomy was performed, and it was found that the duodenum up to the crossing of the mesenteric vessels was definitely dilated, but not to the same degree as in the first case. A small indurated ulcer was seen and felt in the usual position on the first part of the duodenum. It was decided to do a posterior gastro-jejunostomy for the following reasons: (*a*) If the gastric contents were short-circuited into the jejunum, the duodenal obstruction would be insufficient to interfere with the normal course of the bile and pancreatic juices. In other words, the flow up to the obstruction would be cut down to an amount which could pass quite easily. (*b*) A gastro-jejunostomy would be a more certain method of resting the ulcer.

The tip of the appendix was somewhat inflamed and adherent; appendicectomy performed. It would appear that the ulcer in the duodenum showed a distinct tendency to heal, and it is possible that duodenal delay associated with attacks of chronic duodenal ileus was a strong predisposing factor in its recurrence.

I beg to thank Mr. F. J. Steward, Mr. E. C. Hughes and Dr. J. A. Ryle for their kind permission to publish these cases.

APPENDIX

Note on the Treatment of Persistent Post-operative Vomiting

The treatment of persistent post-operative vomiting by continuous evacuation entirely eclipses the usual method of repeated gastric lavage. The latter frequently causes collapse in patients who are already very weak and is, at the best, inefficient, as the stomach refills before it has had time to regain its tone. If the stomach is kept empty by continuous suction for some hours, it will be found that the vomiting will cease, and that the amount that can be withdrawn will become much less. The suction may now be stopped temporarily and the patient allowed to drink a small quantity of water. After a few minutes the pump is again turned on and any fluid that is still present in the stomach is extracted. As time goes on and the patient improves, the suction is stopped for longer periods and the amount allowed by mouth is increased, until at length the stomach regains its tone and is performing its normal functions, when the tube may be withdrawn. In severe cases it is sometimes necessary to go on for days, but lives will be saved. If the patient does not tolerate the tube well it can be removed for a few hours during the night, but it is often found that the patient is less restless with it in although he dislikes it, because in that case the stomach is empty, whereas in the other it is distended.

A further point that has been brought out by this method is that in conditions leading to the persistent vomiting of large quantities of fluid the stomach secretes into its lumen to a greater extent than one would imagine possible in such dehydrated patients. Thus if saline solution is given subcutaneously at a time when but little fluid is being withdrawn by the pump, it will be found that after a few minutes more fluid can be evacuated, and that this increase can again be cut down by stopping the saline injection. Therefore not only are the stomach contents not being passed along, but that organ is further adding to its own distension.

IV. CASE OF DUODENAL ILEUS WITH PERFORATING DUODENAL ULCER

By J. A. RYLE, M.D., Assistant Physician to Guy's Hospital.

I was consulted on May 8, 1923, by a commercial traveller, aged 51. He complained of a gnawing pain in the chest and a

gripping pain around and below the navel which sometimes "doubled him up." He was frequently wakened at night by pain, and the pain was eased by taking food. He also experienced interscapular pain developing at midnight and lasting several hours. Five years previously he had been treated for duodenal ulcer with a satisfactory result. The symptoms when he consulted me had been present for three months. His weight was stationary; appetite not very good; cigarette consumption 100 per week.

I noted some fullness in the epigastrium and guarding of the right upper rectus with tenderness here. There was slight tenderness on deep pressure in the right iliac fossa. Physical examination in other respects was satisfactory. A clinical diagnosis of chronic duodenal ulcer, possibly in association with chronic appendicular disease, was made.

Mr. Magnus Redding examined him with the x-rays after a barium meal and reported as follows:—"Stomach is somewhat dilated. Slight ptosis and hypotonus. Motility is active. Meal leaves freely. There is marked deformity of the first part of the duodenum. Moderate degree of duodenal ileus, the delay originating at the point where transverse portion of the duodenum is crossed by the superior mesenteric vessels.

"6 *hours*.—Stomach empty. Meal in jejunum and ileum. All coils freely mobile. Cæcum filled.

"24 *hours*.—Meal in large gut from cæcum to pelvic colon. Moderate ptosis of proximal colon. Appendix not filled.

"*Conclusions*.—Duodenal ulcer and duodenal ileus. Moderate enteroptosis. No definite evidence as to condition of appendix, as this does not fill."

A fractional test-meal showed a climbing hyperchlorhydric curve. Normal rate of emptying. The free acidity was $75\frac{N}{10}$NaOH at $2\frac{1}{4}$ hours. At $2\frac{3}{4}$ hours 70 c.c. of clear acid juice were withdrawn.

The stools gave positive chemical and spectroscopic tests for occult blood.

As the duodenal ulcer in this case was complicated by duodenal ileus, and the well-marked muscular guarding in the right upper quadrant suggested to my mind the probability of a deep anterior ulcer, I strongly urged the patient to have a gastro-jejunostomy. He declined, however, to have the operation. I told him that I could not accept the responsibility for the results of medical treatment, and I wrote to his doctor insisting that, if medical treatment were employed, it should be carried out strictly and for a long period. In a second letter written to the patient's doctor, the following sentences were included:—"I urged operation because I believe that this is a condition in which healing, under the best possible circumstances, is unlikely to result permanently from medical treatment. When he came to me he had definite muscular guarding over the duodenal area. . . . This probably means that the ulcer is of

considerable depth, and, with the further aggravation of a distended duodenum, that perforation is a possible catastrophe to guard against."

The advice was not followed, and a few weeks later the ulcer perforated.

It would seem that the association of duodenal ileus with ulcer should be included among the absolute indications for surgery.

REFERENCE

[1] Houghton, L. Wynn; Venables, J. F., and Lloyd, N. L.: *Guy's Hosp. Rep.*, lxxv. 147, 1925.

ENTEROSTOMY

By R. P. ROWLANDS, M.S., Surgeon to Guy's Hospital.

ACUTE obstruction of the small intestine is a very dangerous condition, which, in spite of the great advances made during recent years in general abdominal surgery, continues to carry a high mortality. This was just over 32 per cent. in 1655 cases recorded at seven London Hospitals between 1919 and 1925; [1] if the 613 cases of intussusception are excluded, the mortality is nearly 38 per cent.

Delay in diagnosis and treatment is chiefly responsible for the failure to reduce this appalling mortality. The delay in diagnosis is due to the lack of appreciation by the public and by the rank and file of the profession of the significance of the early symptoms and signs: the gravity and urgency of the disease are not sufficiently understood. Treated in time, before the onset of gangrene or paralytic distension of the bowel, intestinal obstruction is easily overcome at a small risk, whereas most delayed operations are doomed to failure, death being due to either chemical or septic poisoning, although the actual obstruction has been relieved.

It is, therefore, of the greatest importance to make the diagnosis and to come to a definite decision at the earliest possible moment, and to apply the only hopeful treatment by operation without delay. The danger increases with every hour that passes, so that the chances of success after three or four days of complete obstruction are very poor. The association of severe abdominal pain, repeated vomiting and complete constipation demands immediate decision and action. If the pain is severe and colicky and is associated with visible peristalsis, if the vomiting is persistent, brown and offensive, and if two enemata fail to produce a proper action, the diagnosis is established and the time for opening the abdomen has come. To wait for a distended abdomen and a quick pulse, and to be misled by the abatement of pain and vomiting is to court disaster. A partial enterocele may mislead by allowing the bowels to act, but the other signs prevail, and this form of obstruction is almost limited to strangulated external hernia, which can be found by careful and repeated examinations of the hernial orifices.

As already stated, an operation carried out in time, before complications have developed, is easy, simple and safe; it is only necessary to reduce the intussusception, to divide the band, to untwist the volvulus or to undo the adhesion or kink. In late cases, however, when gangrene, paralytic distension with the absorption of chemical or bacterial poisons, and dehydration have supervened, things are very different. It may not be possible to reduce an intussusception owing to adhesions or gangrene, and the paralytic distension and poisoning continue in any case. Here the operation is bound to be difficult and tedious, and exhausting both for the patient and the surgeon. If life is to be saved, special plans have to be made and expeditiously carried out: judgment, experience, speed, efficiency and gentleness become priceless. The removal of the cause of the obstruction is of no use if it fails to save life; some quick, certain and efficient method of drainage may be of greater value, at least as a temporary measure.

In the gravest cases, making a fæcal fistula in the distended small intestine under local anæsthesia is the safest and most hopeful plan, just as cæcostomy is the ideal temporary treatment of similar grave obstruction of the colon. In less severe cases, although the cause of obstruction of the small intestine may be overcome, an enterostomy may still be necessary to relieve tension and to prevent further toxic absorption. Often a short-circuit overcomes the obstruction and provides adequate drainage at the same time. It is, however, unwise to leave any gangrenous bowel in the abdomen, it is better to remove it quickly and to join the bowel above and below, and often to drain the upper bowel by temporary enterostomy.

The chief difficulty is in the choice of method for each individual case, *i.e.* to decide when it is necessary to drain the bowel and which is the best method—enterostomy or short-circuit. Occasionally continuous aspiration with Einhorn's tube serves to empty the upper bowel instead of or in addition to an enterostomy.

There is no doubt, however, that enterostomy is the simplest, safest and best method of treating the gravest forms of acute obstruction of the small intestine, and its more frequent use would save many lives which are lost by the adoption of more heroic methods. Frequently the enterostomy cures without the need of a secondary operation to remove the cause of obstruction; for instance, the relief of distension of the bowel above an adhesion often abolishes a kink. Sometimes, however, a secondary operation is necessary to remove the cause of obstruction.

Enterostomy, either alone or in addition to other operations for obstruction of the small intestine, would be far more frequently used if we could be sure that a secondary operation would not be required to close it. The chief object of this communication is to spread the knowledge that such a method is available.

Operation

A temporary valvular enterostomy can be made if necessary under local or, better, under local and regional anæsthesia, a solution of novocain (1 per cent.) being injected subcutaneously around the site of the incision and deeply into the appropriate intercostal nerves as they course between the flat muscles of the flank.

An incision, two inches long, is made through the middle third of the left rectus. Another injection may be made, if necessary, into the parietal peritoneum. After dividing this membrane and displacing the omentum, a distended coil above the obstruction usually presents. If this coil is over-distended and unhealthy, the bowel is traced up to a healthier part and a loop, six inches long, is brought out, emptied and clamped. A small opening is made on the free border, near the lower end, and the end of a soft rubber tube is inserted so that one inch of it lies within the bowel. The tube, the internal diameter of which is one-sixth of an inch, is open at the end and has two side openings; it is fixed by a suture of fine linen thread, which pierces both it and the edges of the intestinal wound, and is tied with a slip-knot so that this can be untied and the tube can be easily removed at any time. The tube is then buried for two inches above the intestinal incision by a continuous sero-muscular suture of fine catgut after Witzel's method of gastrostomy. The outer end of the tube is temporarily tied to prevent leakage while it is passed through the great omentum [2] and a small stab wound which pierces the whole thickness of the abdominal wall at a convenient point, generally above and to the left of the navel. The omentum is fixed to the intestine above and below the tube by two catgut sutures. The omentum not only helps to prevent leakage, but also to preserve the mobility of the intestine. A suture is inserted in the skin and tied round the tube, but it does not pierce the latter for fear of leakage with infection. The main wound is now closed in layers and sealed. The outer end of the tube is placed below the surface of a weak solution of carbolic acid in a jar under the bed. Irrigation of the bowel with normal saline solution can be carried out from time to time, and, if necessary,

food can be given later through the tube. This method of making a valvular opening is much better for the small intestine than the purse-string or "ink-bottle" method of Senn, used with such success for gastrostomy and cæcostomy, for it does

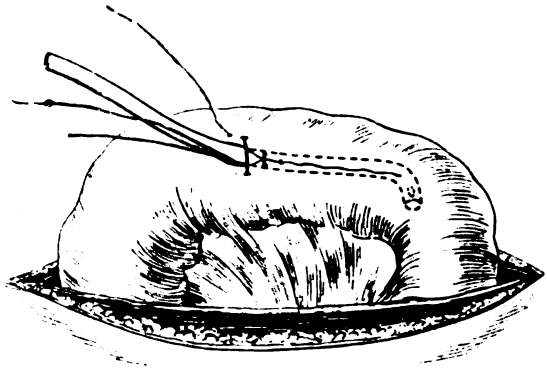

FIG. 1.

not narrow the lumen of the bowel nearly so much while making a most efficient valve.

When vomiting has ceased and the bowels have acted, the tube can be removed after cutting the skin suture and untying the slip-knot, the ends of which project by the side of the

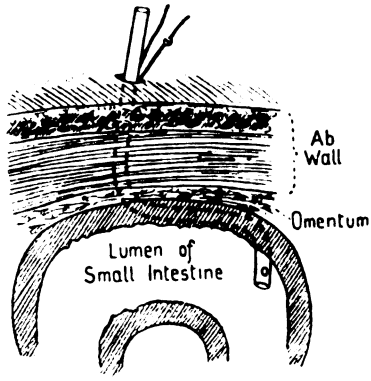

FIG. 2.

tube. Very little, if any, leakage follows the removal of the tube and a secondary operation is rarely necessary to close the fistula.

Some fifteen years ago I helped to save the life of my House Surgeon by performing enterostomy by the purse-string method, closing the fistula with Lembert sutures introduced under local anæsthesia three days later. Since then I have used this and

the improved method described above with excellent results on many occasions.

A boy aged 8 years came under my care when extremely ill and emaciated, suffering from complete obstruction of the small intestine following acute appendicitis, with peritonitis, for which three operations had been performed. The obstruction had been complete for four days with incessant vomiting. The boy was too feeble for a general anæsthetic. Enterostomy was performed through the middle of the left rectus abdominis with the aid of local and regional anæsthesia, and a little ether towards the end of the operation. There was so much plastic peritonitis that it was impossible to deliver a distended coil of small intestine, so that the enterostomy had to be performed in the abdomen. The method of Wetzel being impracticable on account of extensive adhesions, the neck-bottle method had to be used, and the intestine was so friable that the tube only stayed in for two days. The fistula resulted and drained for three weeks, but the bowels began to act naturally at the end of a week, and the fistula drained less and less and finally closed at the end of three weeks, and the boy made a complete recovery. Meanwhile the skin had been protected by castor oil and zinc ointment frequently applied. All who saw this child realised that he was literally snatched from the jaws of death by the enterostomy, and the ceaseless and devoted care of his medical attendant and nurses.

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CHRONIC VOLVULUS OF THE PELVIC COLON SIMULATING PYLORIC OBSTRUCTION, RADIOLOGICALLY DIAGNOSED AND SUCCESSFULLY RESECTED

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

"So the excrements being by degrees very dry, stop the passage against themselves and the wind, and cause the Colick often, but convolvulus sometimes, and other great symptoms."—Fienus, *A New and Needful Treatise of Spirits and Wind offending Man's Body*, 1668.

SIR ARBUTHNOT LANE was the first to show that a volvulus is only the terminal stage of a condition which generally takes years to develop. Chronic stasis in the iliac or pelvic colon

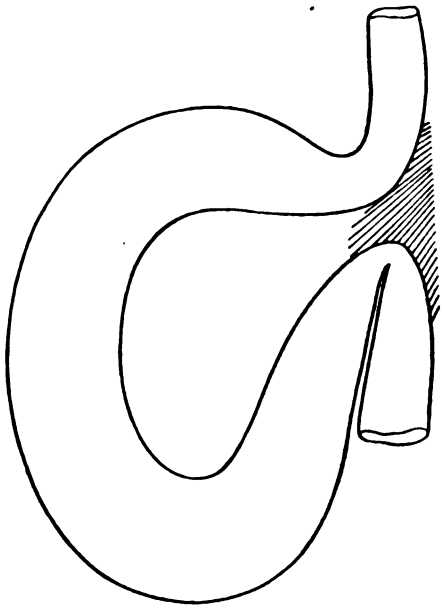

FIG. 1.

Diagram of iliac colon before formation of a volvulus (W. A. Lane).

leads to its elongation and dilatation. At the same time its mesentery becomes greatly elongated (Fig. 1). As this leads to an abnormal degree of mobility, the loop is liable to become twisted. It is, however, rare for an operation to be performed except when a volvulus has led to acute obstruction, the earlier

chronic state in which only incomplete and intermittent obstruction is present generally escaping recognition.

The following case is recorded because a diagnosis was made in the absence of acute symptoms, when surgical intervention could be undertaken with good prospects of success. It is also of special interest, because clinically there were no symptoms of even partial intestinal obstruction, and the visible peristalsis in the dilated bowel was in the position and direction characteristic of pyloric obstruction.

Mr. N., aged 60, was admitted to New Lodge Clinic on November 5, 1925. He had had attacks of colitis with diarrhœa and passage of blood and mucus accompanied by pyrexia in 1904 and 1918, the illness lasting about two months on both

FIG. 2.

Drawing of visible peristalsis in the hypertrophied volvulus, simulating gastric peristalsis.

occasions. Apart from this his health had been good and his bowels had been regular until seven weeks before admission, except for the fact that he had been losing weight since the beginning of the year. In the middle of September he became constipated, passing little except mucus unless he took a purgative, when he had diarrhœa. At the end of the month he had an attack of pain in the upper part of the abdomen, most marked in the left side; this was followed by vomiting, and his temperature rose to 100° F. The illness confined him to bed for ten days, but in the fortnight before he came to the Clinic he was still feeling unwell, though there had been no more severe pain. The possibility of cancer of the stomach or pancreas had been considered before he was sent to us for investigation.

On examining his abdomen very strong peristaltic waves were seen from time to time passing from under the left costal margin to the right and downwards (Fig. 2), though no pain was felt at the time. It seemed obvious that the peristaltic waves were passing along a dilated and hypertrophied stomach

towards an obstructed pylorus. We were therefore surprised to find with the x-rays after an opaque meal that the stomach was normal in size and emptied at a normal rate. It was, however, pushed upwards and outwards by a greatly dilated coil of intestine, which proved to be the true site of the visible peristalsis. At the same time it was observed that the left dome of the diaphragm was pushed upwards to a level considerably above that of the right dome by the same air-containing coil of intestine.

The opaque meal passed without delay through the small intestine and colon to the junction between the descending colon and the iliac colon, and there appeared to be no dilatation

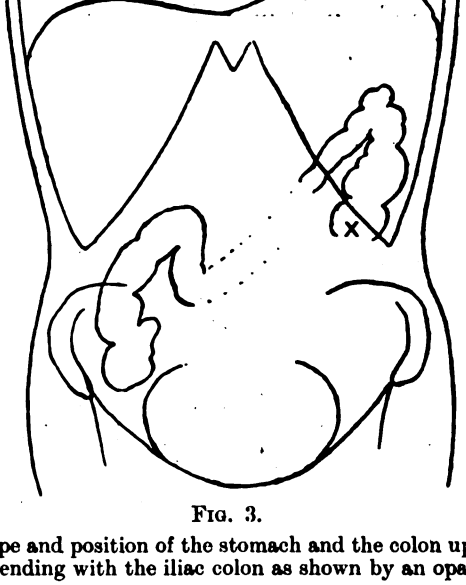

FIG. 3.

Drawing of shape and position of the stomach and the colon up to the junction of the descending with the iliac colon as shown by an opaque meal.

of the intestine up to this point (Fig. 3). The iliac and pelvic colon were not visualised, as at the end of twenty-four hours most of the barium had been evacuated. An opaque enema was then given. This passed without difficulty through the rectum upwards and to the left; in the neighbourhood of the spleen it turned inwards and downwards and the lumen suddenly became narrowed; an inch further obstruction to the enema became complete (Fig. 4). Obstruction just proximal to the splenic flexure would have been diagnosed had not the opaque meal shown that there was no abnormality in the bowel up to the beginning of the iliac colon. As the part of the bowel filled by the enema continued in an almost straight direction upwards to the left from the top of the rectum, it was concluded that this must be the distal part of the pelvic colon, which had been pulled upwards by the distended loop formed

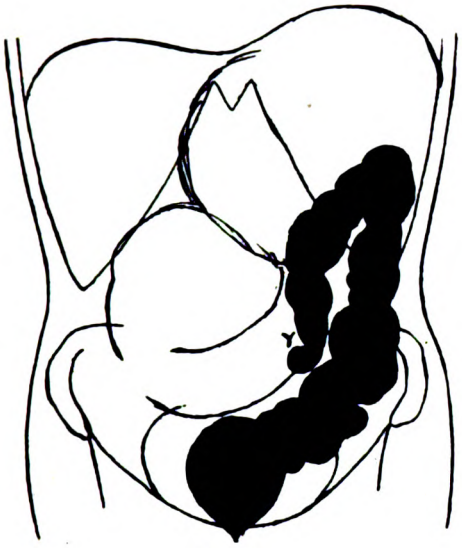

FIG. 4.

Drawing of rectum and pelvic colon as shown by an opaque enema together with the air-containing volvulus.

by the proximal part of the pelvic colon. Subsequently it was shown that the iliac colon and not the proximal part of the pelvic colon was involved; the root of the loop would

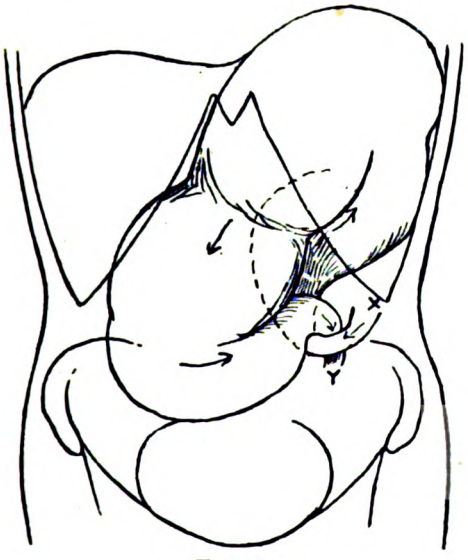

FIG. 5.

Drawing of supposed volvulus of pelvic (or iliac) colon, made before the operation to fit in with Figs. 1, 2 and 3, and confirmed at the operation. X corresponds with X in Fig. 3, and Y with Y in Fig. 4.

therefore correspond with the root of an abnormally developed mesentery of the iliac colon, the distal end being Lane's "last kink."

A chronic volvulus was diagnosed. The drawing reproduced in Fig. 5 was made to explain how the peristaltic waves passing from left to right in the epigastrium could occur in a volvulus of the pelvic or iliac colon with its root in a situation indicated by the point where the passage of the opaque enema was obstructed. The enormous distension of the loop had apparently caused it to rise out of the pelvis and drag the remaining part of the colon upwards and to the left, so that the root of the loop was situated on a level with the iliac crest. The visible peristalsis must have been in the middle part of the loop, so that its natural direction would be from left to right, the peristalsis in the proximal and distal segments, which would be upwards and from right to left respectively, being invisible owing to their deeper situation.

The fact that the stools contained no occult blood was a further point in favour of a chronic volvulus and against a growth. The history, taken with the remarkable contrast between the normal rate of evacuation of the opaque meal and the complete obstruction offered to the opaque enema, showed that the volvulus, though occasionally complete, was more often to a great extent untwisted.

An operation was performed by Mr. Arthur Cooke of Cambridge on December 16, 1925. A dilated and hypertrophied loop formed by the iliac colon was found; it looked as if it might have been the seat of repeated volvulus. Its mesentery was greatly elongated, measuring 9 or 10 inches at its longest diameter; in several places it showed silvery scarred lines, apparently secondary to the old colitis. The loop was excised, and the bowel was brought together by a side-to-side anastomosis. The loop, after it had become cold and shrunk, measured 17 inches in length and 4½ inches in diameter. The patient made an uninterrupted recovery, and, when last heard from, on March 18, 1926, he was very well.

BALL-VALVE ACCUMULATIONS IN THE RECTUM

By J. A. RYLE, M.D., Assistant Physician to Guy's Hospital.

THE impaction of hard and bulky fæces in the rectum, particularly in the case of aged and infirm persons, has long been reckoned among the causes of severe constipation. Digital or instrumental fragmentation and removal of the fæcal mass is the accepted treatment when enemata are unavailing. Occasionally the mass becomes moulded into the shape of a ball or ovoid, which distends the rectum and, while sufficiently mobile to allow the escape of flatus or fluid material, itself resists all natural efforts at expulsion.

Hurst [1] devotes a chapter of his book on Constipation to this type of disorder, and on p. 258 describes the case of a child aged four who came under his observation with an unusually large colonic accumulation above a movable globular mass weighing a quarter of a pound. He refers to a description of similar accumulations in old subjects by Curling [2] (1876), and accords to Simpson [3] (1849), who specifically employs the term "ball-valve," the priority for having furnished the first account of the condition. A still earlier account is to be found in the writings of William Heberden,[4] who, in a single brief paragraph, aptly depicts the main symptoms and complications as follows: "The fæces sometimes lie in the rectum for many months, and are collected into a large hard mass, which cannot be voided without the help of a surgeon. The signs of this are, pains in the belly; a constant desire to go to stool, even just after an evacuation; none but liquid fæces are ever voided; and the disorder is attended with a difficulty of making water."

During the past few years seven examples of this condition have come to my notice. These might appear altogether too trivial, and the nature of the symptoms too obvious, to be worth recording, but I am persuaded to do so for the following reasons:

(1) In six of the seven cases the cause of the symptoms had passed unrecognised by the medical men and nurses in attendance. Three of these cases (Cases 2, 5 and 7) were under close observation in hospital. The seventh patient was a medical man who was able to appreciate the cause of his discomforts.

(2) The direct or complicating symptoms in five of the

cases were so severe and distressing as to call urgently for relief and in three cases (Cases 3, 4 and 6) had prompted a suspicion of some more serious malady.

(3) In three cases (Cases 1, 2 and 7) the trouble was a direct result of an x-ray examination with barium meal or enema, and the accumulation was largely composed of barium sulphate.

In the histories of the first three cases there is nothing particularly noteworthy.

Case 1

A medical man, aged 64, had an obstructive carcinoma of the splenic flexure. He had been examined with a barium enema in order to locate the point of the obstruction. During the ensuing forty-eight hours he expressed himself as unable to void the "cement-like" accumulation by natural efforts, and was compelled to relieve himself digitally.

Case 2

A lady, aged 60, had undergone a routine examination of the alimentary tract after a barium meal. A day or two later she was in great discomfort, and this the nurse had been unable to relieve with enemata. Rectal examination revealed a globular, putty-like mass in the rectum, which could be moved about by the examining finger and which had to be broken up before relief could be obtained.

Case 3

An old man was sent to my Out-Patients for chronic diarrhœa and was suspected of having a malignant growth of the bowel. Rectal examination revealed a similar collection of putty-like fæces obviously acting as a ball-valve.

In each of the four remaining cases there were special features which warrant a fuller description.

Case 4

A marine engineer, aged 39, had been out of employment for two years and often rather short of food. He eventually obtained work on a tramp steamer on which the sanitary conditions were poor, and while on a voyage to Gibraltar experienced pain in the lower abdomen which developed an hour after food. This became worse and worse each day, and at Gibraltar he was put ashore and sent to hospital with a diagnosis of gastric ulcer. He lost his pain after three days on a milk diet and was later invalided home. When I saw him he stated that ever since admission to the hospital he had

been troubled with constipation, defæcation had been very difficult, and he had always felt as if the bowel contained something more to be voided. His weight, which had been 10 st. 7 lbs. for years, had fallen to 8 st. The abdomen was everywhere slightly distended and tympanitic, but nowhere tender, and nothing unusual was felt excepting for a resistance rather like a full bladder above the pubes. Rectal examination revealed an enormous fæcal accumulation acting as a ball-valve and obviously accounting for his rectal discomforts. The examination caused great pain. A small amount of the accumulation was removed digitally and immediately afterwards he had the most successful action of his bowels that he had had for weeks. During the next few days the bowel was cleared with the help of enemata and all his symptoms disappeared. He was then admitted to hospital for a routine examination of his alimentary tract. No signs of disease were found. He remained well, and rapidly gained weight.

Case 5

An elderly and obese woman was admitted to Guy's Hospital under my care on account of glycosuria. Shortly after admission she began to complain of pain in the lower abdomen and rectum and developed complete retention of urine. On account of this latter symptom I was asked one day to see her by my House Physician. Catheterisation had then been necessary for twenty-four hours. I suspected a rectal accumulation, and examination revealed a globular mass acting as a ball-valve. The examination was very painful. The mass was broken up under an anæsthetic and the pain and retention were relieved.

Case 6

I was called to see a case in consultation with the following history:—The patient was a woman aged 60. She had been under observation during the past two years for dyspeptic symptoms with epigastric and subscapular pains. Two weeks previously she had vomited a little blood. A week later she had a more definite hæmatemesis, became collapsed and afterwards passed large tarry motions. As the colon seemed to be overloaded, she was ordered enemata, which at first brought away some rather solid material but later were returned clear. For the last four or five days she had been complaining of constant pain in the rectum, pain in the lower abdomen, "bearing down" sensations, and much anxiety and misery. Her doctor was afraid that she might have some malignant disease of the bowel. The patient, who was a multipara, stated that "the pains were like bad labour pains." She also had pain on passing water. There was moderate tenderness over the lower abdomen, more particularly on the left side, where there was a sense of deep resistance suggesting a greatly distended

pelvic colon. Rectal examination showed an enormous ball-valve accumulation of fæcal material, hard, with a greasy surface, receding before the examining finger, and feeling in shape and size not unlike a fœtal head. The examination caused intense pain. On the next day she was given an anæsthetic, the accumulation was broken up and removed by lavage with prompt relief of all her symptoms.

Matthews Duncan [5] reported a very similar case in which the patient had been thought to be dying of a rectal carcinoma.

Case 7

A man, aged 63, was sent to me on account of a large hard tumour in the epigastrium. There was also a gland above the left clavicle and a swelling of the right testicle. It was eventually decided that the mass in the epigastrium consisted of retroperitoneal deposits from a malignant growth of the testicle, but in the early stages steps were taken to exclude a primary alimentary carcinoma. For forty-eight hours or more after the x-ray examination patient was in the greatest distress, had frequent and urgent calls to stool, and much "bearing down" pain. Within the space of twenty-four hours he visited the lavatory on thirty occasions, but was never able to pass more than a very small amount of semi-fluid material. He was in hospital and had been treated with purgatives or enemata without result. Neither the resident medical officer nor the Sister was familiar with the symptoms. Rectal examination showed a large globular mass in the rectum with a greasy surface; it was extremely hard, and consisted mostly of barium. The examination caused exquisite pain. The mass was finally broken up under an anæsthetic and cleared away with enemata.

It should be noted that with one exception these patients were aged sixty years or upwards. Doubtless their age or infirmity had combined to diminish the expulsive power of the rectal muscles. The clinical symptoms cannot be more concisely described than in the words of Heberden quoted above, but it is necessary to have witnessed the sufferings of these patients to appreciate how severe they may be. Case 6 likened her sensations to "bad labour pains," and their rhythmical recurrence during the examination was very reminiscent of the pangs of childbirth. In Simpson's cases [3] also the pains were likened to those of labour. Case 7, a very plucky man who bore his illness bravely, suffered great misery and made as many as thirty attempts to empty the bowel in the course of one day. The pain is felt both in the rectum and in the lower abdomen. Presumably as the result of reflex anal spasm the rectal examination in every case caused great pain resembling that

induced by rectal examination in cases of anal fissure. The factors which prevent the evacuation of these fæcal masses would seem to include their solid consistency, spherical shape, and smooth greasy surface. In three instances (Cases 2, 6 and 7) the doctor or nurse in attendance had been deceived into thinking that there could be no rectal accumulation because enemata had been returned clear.

Summary

The Causes, Symptoms, Diagnosis and Treatment of ball-valve accumulations of fæces in the rectum may be summarised as follows :

(1) *Causes.* (*a*) A recent gastric or duodenal hæmorrhage, a barium meal or enema, or a milk diet. These may impart such a consistency and superficial greasiness to the fæcal mass as to render it difficult of passage. (*b*) Dehydration as the result of recent hæmorrhage, or of fasting or diabetes. Any of these may help to make the stools unnaturally solid, while the long sojourn of the mass in the rectum results in further desiccation. Robson[6] described six cases of "acute fæcal impaction in the rectum" consequent upon diarrhœa or hæmorrhage. (*c*) Old age or infirmity. These combined with the fatigue of repeated calls to stool and reflex anal spasm diminish the expulsive power of the muscles of defæcation.

(2) The *Symptoms* include : (*a*) Frequent and urgent calls to stool with no result or small fluid results. (*b*) A feeling after evacuation as though there were still something further to expel. (*c*) Severe recurring pain of a peristaltic kind (rectal colic) and lower abdominal colic. (*d*) Painful anal spasms which are intensified by digital examination. (*e*) Difficulty of micturition or actual retention of urine. (*f*) Failure to give relief by purgatives or enemata unless the mass be first broken up.

(3) The *Diagnosis* is at once made by a digital examination. This reveals a large solid, putty-like globular mass, which often recedes from the examining finger and, owing to its slippery surface, may be difficult to grasp.

(4) *Treatment* consists in the fragmentation and piecemeal removal of the mass and clearance of the rectum by repeated lavage. For this operation the administration of an anæsthetic is usually necessary. As a preventive measure it should come within the province of the radiologist to advise proper supervision of the evacuations in old or feeble persons who have been subjected to examination of the alimentary tract after a barium meal or enema.

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SALICYLATES IN GALL BLADDER DISEASE

By F. A. KNOTT, M.D., Pathologist to New Lodge Clinic.

THE use of sodium salicylate as a biliary antiseptic was first suggested by Kuhn [1] in 1904. It had previously been stated by several observers that, taken by the mouth, salicylates were rapidly excreted in the urine, largely as salicyluric acid, and also in small quantities from the large intestine and in the bile, sweat and saliva. Since 1904 a variety of salicyl compounds have been introduced for internal administration, and the same general mechanism of salicylate excretion has been confirmed by Stockman.[2]

Cartier [3] also proved by observations upon cases of biliary fistula that salicylate is one of the most powerful excitants to biliary excretion, the increase affecting not only the volume of the bile but also its bile-salt and cholesterol content.

Chauffard [4] has recently reviewed this work, and notes that in his clinical experience salicylate by itself is beneficial in cases of painful, non-infected cholelithiasis only, and prefers to combine this treatment with a course of urotropine when the gall bladder is infected.

Some experimental evidence in support of this use of urotropine has been put forward in a previous note,[7] and Hurst [5] has further shown that very large doses of this drug (up to a 100 grains three times a day) are generally well tolerated if alkalis are given at the same time, rendering the urine alkaline and thus preventing vesical irritation.

But as one still meets with cases of gall bladder infection in which salicylates only have been employed, it seemed worth while to estimate by laboratory methods the amount of biliary antisepsis which might be achieved in this way without the use of urotropine.

From the work of Chauffard and Cartier mentioned above it may be assumed that the cholagogue effect of salicylates is established, but before discussing the antiseptic effect it will be well to recall the action of the gastric and other digestive juices upon those salicylates most commonly prescribed.

Llewellyn Smith [6] has shown that acetyl salicylic acid in passing through the normal gastric juice is split up to an extent

of not more than 5 per cent., the remainder being hydrolysed and absorbed in the small intestine as salicylate. It was found by Stockman that phenyl salicylate (salol) and most similar compounds pass the gastric acidity practically unchanged and are then hydrolysed, and that salicylic acid and sodium salicylate reach the small intestine to be absorbed as alkaline salicylates. Thus when hydrolysis of these salicylate compounds occurs, it is in an alkaline medium, and alkaline salicylates enter the circulation. When they reappear in an alkaline excretion, they are still present as salicylates, and only in a definitely acid excretion are small amounts of the free acid present.

It has therefore seemed justifiable to use, in the experiments upon the bacterial inhibition in bile, solutions of sodium salicylate, whereas in the tests upon living animals various members of the salicylate group of compounds have been employed.

Quantitative Excretion of Salicylate in Bile

To obtain some indication of the strength in which the drug might be made to appear in naturally excreted bile, adult healthy guinea-pigs received by the mouth, three times daily for one to three days, doses of salicylic acid, salol, aspirin and sodium salicylate. The quantities administered, taking into account the average body weights of the animals (350 gm.), and man (70 kilogm.), corresponded to at least four to five times the maximum pharmacopœial dose. The animals were killed on the second or third day and the bile immediately removed from the gall bladder by puncture with a fine-pointed glass teat pipette. The bile was then run into small-bored sedimentation tubes, and a little 10 per cent. ferric chloride solution added, so that the liquids made a sharp line of contact half-way up the tube. When salicylate was present in the bile, the well-known purple colour developed as a ring which diffused both upwards and downwards, its density being observed after one minute by transmitted light. By preparing beforehand tubes of guinea-pig bile containing known amounts of salicylate and adding the ferric chloride to all the tubes at approximately the same time, it was possible to make the test roughly quantitative for the amount of salicylate present in the bile of the experimental animals. Bile containing 0·002 per cent (1 in 50,000) sodium salicylate was found to give a just visible colour, and was the highest dilution at which certain detection was possible.

The results may be tabulated as follows :—

TABLE I.

No. of animal.	Duration of dosage.	Doses of salicylate compounds.	Approximate strength of salicylate in bile obtained.	
			As dilution.	As percentage.
1	2 days	Sod. Salicylate 0·04 gm. t.d.s.	Not detected.	Less than 0·002%
2	1 day	,, ,, 0·05 gm. ,,	1 in 25,000	0·004%
3	3 days	,, ,, 0·04 gm. ,,	1 in 50,000	0·002%
4	2 days	,, ,, 0·04 gm. ,,	1 in 50,000	0·002%
5	2 days	Salicylic Acid 0·03 gm. ,,	1 in 25,000	0·004%
6	1 day	,, ,, 0·05 gm. ,,	1 in 25,000	0·004%
7	2 days	,, ,, 0·03 gm. ,,	1 in 50,000	0·002%
8	2 days	Aspirin 0·02 gm. ,,	Not detected	Less than 0·002%
9	2 days	,, 0·04 gm. ,,	1 in 50,000	0·002%
10	2 days	,, 0·03 gm. ,,	Doubtful. Less than 1 in 50,000	Less than 0·002%
11	3 days	Salol 0·03 gm. ,,	Doubtful. Less than 1 in 50,000	Less than 0·002%
12	2 days	,, 0·04 gm. ,,	1 in 50,000	0·002%

Antiseptic Effect of Salicylate

The lethal and inhibitive powers of sodium salicylate towards bacteria were first tested in nutrient broth and in bile taken from recently removed human gall bladders kindly given to me by Mr. R. P. Rowlands. Using the technique described in a previous note[7] on bacterial growth in bile, but substituting a 25 per cent. solution of sodium salicylate for urotropine, it was found with bile that in strengths weaker than 0·25 per cent., no definite inhibition of the growth of various strains of *B. coli* could be detected. With *B. typhosus* as the test organism, the minimum strength at which satisfactory inhibition could be observed was 0·075 per cent. Using even 1 per cent. sodium salicylate in bile, *B. typhosus* did not die out in this medium during three days' incubation at 37° C.

Substituting nutrient broth for bile in the above experiments, the corresponding figures for demonstrable inhibition of bacterial growth by sodium salicylate were, for *B. coli* about 0·35 per cent., and for *B. typhosus* 0·1 per cent. As in the case of urotropine, there seemed to be some evidence that inhibition was slightly more effective in bile, but the necessary concentration of salicylate is relatively so high in both cases that, as will be seen from the next paragraph, it is doubtful whether this difference is of any importance from the standpoint of practical therapeutics.

Summary

As far as can be judged from these animal experiments, the average concentration of sodium salicylate in the bile after oral

administration in pharmacopœial doses of any of the salicyl compounds used is not above 0·002 per cent. to 0·003 per cent.

The experiments *in vitro* with known concentrations of sodium salicylate in bile suggest that a strength of at least 0·1 per cent. would have to be attained before any satisfactory bactericidal effect would be produced in the biliary tracts.

The difference between these two concentrations is so great that it seems very doubtful whether oral administration of salicylate compounds alone can result in any satisfactory degree of biliary antisepsis.

In conjunction with the experiments previously made upon the value of urotropine in biliary infections, the present observation supports the view of Chauffard that administration of salicylate compounds alone is chiefly useful in cases of non-infective cholelithiasis, and that urotropine should be used when infection of the gall bladder is likely or known to exist. Urotropine should, however, be given according to the technique devised by Hurst, which makes it possible to administer a dose about seven times as large as that recommended by Chauffard.

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TWO CASES OF SECONDARY SARCOMATOUS DEPOSITS IN THE CEREBRUM

By J. G. WESTON.

In the first of these two cases, interest centred round the contrast between the clinical diagnosis, apparently confirmed at autopsy, and the final microscopic decision. The second case presents many points of similarity in the clinical story and pathological findings, so that a review of the two together is of some interest.

Case 1.—A man, aged 46, was first in Guy's under Dr. A. P. Beddard from February 23 till April 4, 1925. He had attended medical out-patients since February 8 for pain in the right side of the chest with bronchitis, but no other history could be obtained. He had expectorated a moderate amount of thick yellow sputum, non-nummular in character. Briefly his physical signs were those of fibrosis in the upper lobe of the right lung with consequent shifting of the heart. The nervous system was normal.

The x-ray appearance suggested that the condition was a tuberculous one, though the length and nature of the history were quite atypical, and the localisation strictly to one lobe unusual. Specimens of sputum on three occasions contained no tubercle bacilli. The cutaneous tuberculin reaction was strongly positive for bovine tuberculosis. *Streptococcus longus* was isolated from the sputum and he was treated with a vaccine prepared from it.

On March 18, after having been depressed for some time with a suicidal tendency, he had a Jacksonian epileptic fit, starting in the left arm, and spreading to the left side of the body and to the right hand in forty-five seconds. He then was cyanosed and comatosed, and chloroform was used to control him after four fits. It was necessary to transfer him to the strong-room, and after coming round he was maniacal. The Wassermann reaction of the blood was negative. On April 4 he went home, improved physically and mentally. The diagnosis was fibroid phthisis.

He returned on July 29 to the neurological out-patients department with a right frontal and suboccipital headache, which he had had since the beginning of July. He was admitted under Dr. C. P. Symonds on August 25, when the headaches had become continuous and allowed him but a few hours' sleep. In July and August he had experienced seizures with coarse

tremors of the left hand and arm, and sometimes the leg. He had had vertigo, and had been nauseated but had not vomited.

When admitted he was irritable and restless. Whereas when under Dr. Beddard the pulse rate had varied from 80 to 70 with normal temperature, now it was 60 to 50. His lung condition was as before. The reflexes of the left side were now exaggerated and the lower left abdominal absent. Ankle clonus and extensor plantar reflexes were bilateral. His discs now presented papillœdema; his Wassermann was again negative, and the sputum contained no tubercle bacilli.

A radiogram of his chest was reported as "showing infiltration of the right apex of a flocculent nature, suggesting phthisis." The x-ray examination of the skull showed no abnormality, the sella turcica being rather large.

A diagnosis was made of a cerebral tumour in the right motor cortex, possibly a tuberculoma or a secondary abscess from the lung. Dr. Marshall saw the man and considered the "chest condition almost certainly phthisis without bronchiectasis."

On September 10 Mr. L. Bromley operated; he exposed the brain in the region of the right precentral gyrus by a bone flap three inches in diameter. No tumour was found, but a milky appearance of the vessels was observed with marked congestion and signs of increased intracranial pressure. The neighbouring gyri were explored with a stilette, but no differences in consistency were found. Mr. Bromley left the brain decompressed.

After the operation the patient was never in a very satisfactory condition. He was conscious of questioning and could give a moderately intelligent answer, but at other times he was in a stuporous state. He became incontinent of urine, developed cystitis and died on October 17.

Dr. Marshall performed a post-mortem the next day. What at first was taken to be a caseating gland in the right upper lobe of the lung was found microscopically to be a spindle-celled sarcoma of the eparterial bronchus. The compression and obliteration of the bronchus had sharply marked off the upper lobe from the rest of the lung. What first appeared to be phthisical fibrosis with dilatation of the bronchi containing muco-purulent secretion proved to be fibrosis and bronchiectasis resulting from compression. No other parts of the right or the left lung were abnormal.

In the brain a red fibrinous patch represented the decompression site, but no tumour was present in the right Rolandic area. A tumour the size of a golf ball was, however, found in the right frontal lobe. This was necrotic and had the typical naked-eye appearance of a caseous tuberculoma. But further section presented a larger, deeper tumour in the right cerebral hemisphere, almost obliterating the lateral ventricle and pushing the septum to the left. Similar smaller tumours were found deep in the left frontal and left occipital lobes. No other tumours were found in the body. The tumours of the brain were found on microscopical examination to be spindle-celled sarco-

mata completely necrosed except for a little neoplastic tissue round the new-formed vessels.

Perhaps the most striking feature of the autopsy was the tentative confirmation of phthisis and cerebral tuberculoma till microscopic sections showed the true pathology.

Case 2.—The second case is that of a woman admitted under Dr. Symonds in 1921. In the cerebral hemispheres again were secondary growths, circumscribed and spherical, which on section proved to be sarcomatous. The primary tumour appeared to be in the left ankle and was relatively insignificant, although it had caused vague symptoms for approximately two years.

The woman was admitted for weakness of the right arm. She had, eight years previously, when forty-five, had a hysterectomy for fibroids. Two years before admission she had noticed pains in her left foot, and eight months previously had been treated in the orthopædic department of another hospital for flat foot and had been ordered a special boot. The weakness of the right arm developed three weeks before admission. When first seen she had weakness of an upper neuron type affecting the right side of the body, with extreme plantar reflex, together with sensory loss of cerebral type. Under observation she became drowsy though irritable. She developed swelling of the optic discs. Later weakness and stiffness of the left arm developed and the left plantar response became extensor.

At the end of a month swelling was observed in the left ankle joint, and an x-ray plate showed " bony changes affecting the bones of the left foot and lower part of tibia and fibula; the scaphoid bone and head of the astragalus on the inner side are also partly absorbed."

A week later Mr. W. H. Ogilvie explored the ankle joint and found the astragalus partly replaced by some lobulated fatty-looking material which he removed. Dr. G. W. Nicholson reported that this tissue was an angeio-sarcoma " consisting of columns of angeioblasts which are infiltrating the bone."

The patient died sixteen days later, having previously become more lethargic.

At the post-mortem nodules of secondary growth were found in the right lung and the thyroid as well as the brain. These were presumed to be secondary deposits from the angeio-sarcoma, which was found to have affected the astragalus only. The scaphoid was normal.

I am greatly indebted to Dr. Symonds for his notes of the second case and for his help in the preparation of this paper.

STUDIES ON TUMOUR FORMATION

By G. W. NICHOLSON, M.D., Lecturer in Morbid Histology, Guy's Hospital.

IX. THE MIXED TUMOURS (*continued*)

2. *Ectopic Endometrial Tumours* or *Ectopiæ Endometriodes.*—I propose to discuss a species of tumour in this study which is receiving much attention from German pathologists at the present time, as well as from gynæcologists in this country and America, but which has scarcely been noticed by British pathologists as yet. This is the so-called "endometrioma" or "adeno-myoma" of uterine tissue that is found outside the ducts of Mueller. This tumour is of double interest in addition to its clinical importance. In the first place its structure, when fully developed, is identical with that of the endometrium, and so are its functions, if we can judge these from histological structure and clinical behaviour. I may have exceeded the limitations of the histological method in the "identification of normal and tumorous growth" and the "assumption of functional from structural identity" in my writings, but I feel that my arguments are strengthened by the behaviour of the tumours under consideration. It is the function of the endometrium to be shed in part and regenerated at every menstrual period. What better proof is needed of identity than to show that these tumours do so too? In the second place the presence of functioning endometrium at all sorts of spots inside the abdominal cavity and in its walls is difficult to "explain." To be honest, it has not yet been "explained" in spite of the theories which, although they claim to reveal the truth, succeed merely in distorting and obscuring it. It can do us nothing but good to examine these theories and point at their shortcomings, and to humble ourselves and confess our ignorance of the true "explanation."

Before we describe these tumours we must discuss their nomenclature briefly. The time-honoured word "adeno-myoma" is a very poor description of them, since they often contain no muscular tissue. Again, the word "adenoma" implies a certain degree of atypical proliferation of epithelium. This is absent from our tumours, since their structure is that of the physiological endometrium, distorted perhaps, but

never obliterated by the minor differences which are inseparable from the new and often quite unnatural environment in which they are accommodated. The word "endometrioma," proposed by Prof. Blair Bell, does not suffer from these disadvantages, since it does not commit us to a definite histiogenesis, if it be used in a purely descriptive sense.* But when we use the suffix "oma" we commit ourselves to the implication that an anomaly is a true blastoma. The majority of continental writers make use of a word ending in "osis," *e.g.* the "fibro-adenomatosis" of Lauche,[41] implying that the anomaly is a hyperplasia and excluding it from true tumours. I cannot get away from the question: Are the anomalies we are considering tumours in the generally accepted sense of the term? We must, as I have pointed out in Study I, ask ourselves this question in many other cases if not—paradoxical though it seem—in all tumours, but rarely so insistently as here. I have used the word "tumour" advisedly throughout these studies without giving it a definition, nor can I give one now. The word "tumour" possesses a good deal of elasticity, since it means no more than a "swelling" or "lump." "Endometrial tumour" is the most non-committal term I can think of, since it can be used descriptively and interpreted: "A mass of tissue with the structure of the endometrium." I use it in this sense.

Diffuse or isolated tissue, the structure of which is identical, or almost identical, with that of the uterine mucous membrane, is found in many parts of the abdomen: within the uterus and Fallopian tubes, on the peritoneal surface of these organs, in the vagina, Douglas' pouch, the ovaries, the ovarian and uterine ligaments, the groins and labia majora, the wall of the intestines, the umbilicus, and within laparotomy scars. It is found exclusively in women of the child-bearing age and, whenever the clinical history is known, it is associated with disturbances of menstruation. No cases have been recorded in children and only a few atypical ones in old women. These tumours are unknown in males in one or other of the situations possible in this sex.

These endometrial tumours constitute an exceedingly well-defined group histologically, since they reproduce the structure of the endometrium with extraordinary fidelity. They are remarkably "organoid" microscopically and even surpass many teratomata in this respect. They furnish unmistakable

* We have recently been treated to "Muellerianoma" by Bailey,[4] who applies it to certain tumours of the ovaries. I reject this word with protests. A bastard word, misbegotten of no less than three languages, German, Latin and Greek, is too much even for these degenerate times, or so I hold.

anatomical and clinical evidence that they perform the physiological functions of the uterine mucous membrane.

Certain adenomyomata of the gastro-intestinal tract are automatieally excluded from this paper. They contain tubules and cysts lined with more or less columnar epithelium. These are surrounded by bundles of hypertrophied intestinal muscle, without the interposition of the cellular stroma characteristic of the endometrium. They often contain more or less perfect pancreatic acini. They are, therefore, to be regarded as instances of accessory pancreas, the ducts of which have undergone dilatation coincidently with atrophy of the secreting parenchyma. They act upon the intestines as "foreign bodies" and induce hypertrophy of the muscle as a result of its unsuccessful efforts at their expulsion. Stewart and Taylor,[82] who have recently investigated these tumours, show that they generally contain undifferentiated epithelium, the proliferation of which is responsible for their continued growth. These and similar anomalies, described fully by Lauche,[44] are characteristic examples of Albrecht's [1] hamartomata, since they are malformations, the cells of which exhibit a slight degree of independent growth. They differ from the endometrial tumours in that they are generally developmental malformations, whereas most, if not all, the latter are almost certainly acquired.

Endometrial tumours are divided—simply and solely because of their topographical relations—into *internal*, and *external* or *heterotopic* examples. The former originate within the substance of the uterus and Fallopian tubes, the latter, which are further subdivided into *intra-* and *extra-abdominal* tumours, in connection with the serous surfaces of these organs and of other abdominal viscera or within the substance of the abdominal walls.

I do not propose to discuss the internal tumours in this paper. They are very well known and I have no new facts to bring forward in respect of them. They are chiefly of interest for me because they gave rise to long-continued and acrimonious discussions. v. Recklinghausen,[68] as is known to everyone, defended their origin in remnants of the Wolffian body in his classical monograph. His views were, however, soon disputed. Significantly enough it was he himself—in a truly scientific spirit and with an honest desire for the truth—who was the first to show that they may and do arise in uterine epithelium. This he did, in an appendix, upon the strength of a diffuse submucous uterine "adeno-myoma" which he had examined whilst his monograph was in the press. I believe that practically all pathologists are now agreed upon the endometrial origin of these tumours. The only difference of opinion which remains is whether they should be regarded as the result of acquired hyperplasias or congenital malformations of the mucous membrane

of the uterus and Fallopian tubes. Schridde and Schoenholz [79] have recently described many anomalies of the tubes which they believe to be congenital and to form the nucleus of these tumours. I must leave the question open here. To discuss it would be to repeat much of what I have said in earlier studies.

Fig. 81 is a drawing of the histological appearances of a diffuse " adeno-myoma " of the uterus in a woman 46 years of age. It represents an area of uterine tubules embedded in the characteristic stroma. It is surrounded by hypertrophied uterine muscle. The tubules were shown to open into the cavity of the uterus and the stroma was continuous with that of the endometrium.

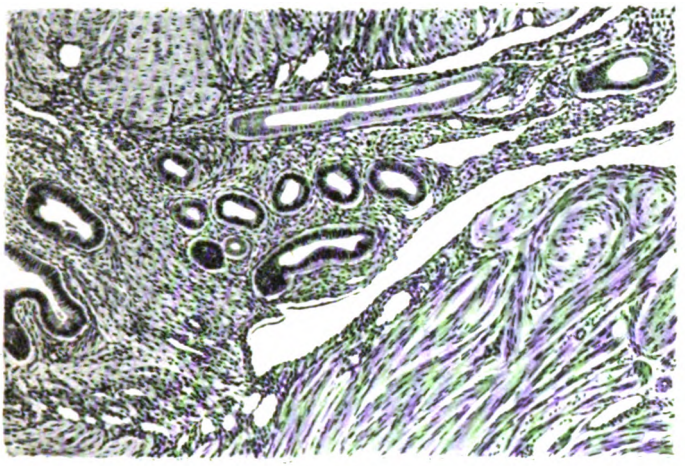

FIG. 81.

Internal endometrical tumour of uterus. Uterine tubules and stroma, and dilated lymph spaces surrounded by hypertrophied muscle. Magnif., 90.

I propose to begin with the extra-abdominal tumours, since they are usually solitary and therefore more suitable for throwing light upon questions of histiogenesis than the intra-abdominal cases, which are often multiple or even generalised and of more interest for gynæcologists than pathologists. The list of references at the end of this paper does not claim to be complete, especially not in so far as the intra-abdominal tumours are concerned. These have been discussed in almost countless publications and summarised by Lauche,[45] Schindler,[77] and others, as well as by Haeuber,[28] who gives a useful, although by no means complete, *résumé* of the British and American literature.

I must intercalate a description of the minute anatomy of the endometrium and of these tumours in general, and reserve

detailed descriptions for individual cases. I follow Schaffer's [75] teaching of the histology of the normal uterine mucosa in the following paragraphs, and recommend his excellent text-book to the notice of English histologists.

It is the function of the endometrium to furnish a suitable soil for the embedding of the ovum, in case it be fertilised. This function is prepared for at every menstrual period by desquamation and death of the superficial parts of the mucous membrane and regeneration of its deeper layers to produce a new one. It follows from this that its structure is in a constant state of change throughout the child-bearing period. Certain phases are distinguished which, of course, merge with each other. These are: the interval, or stage of quiescence, the pre-menstrual, the menstrual, and the post-menstrual stages.

In the stage of quiescence the mucous membrane is lined with a single layer of columnar or cubical epithelium, prolonged outwards as simple tubular glands. These are set somewhat widely apart, are slightly twisted upon themselves,* and extend here and there into the muscular coat. The epithelium is non-ciliated but, as menstruation approaches, it partly acquires cilia, both on the surface and in the glands. The stroma is very cellular and highly characteristic. It is composed of closely packed round, oval, spindle-shaped, and irregular branched cells with large nuclei. A delicate and scanty network of areolar fibres is present between them. It is very vascular, but most of the vessels are collapsed and therefore not easily seen. The *mucosa* is continued into the uterine muscle, which is the hypertrophied *muscularis mucosæ*. Its fibres project into it, between the bottoms of the glands, but do not form sheaths or tunics for them.

In the pre-menstrual stage the glands undergo dilatation. Their epithelium proliferates and projects into the lumina as small papillæ, so that a serrated appearance is produced. The stroma is œdematous from exudation of fluid from the vessels. Its cells are widely separated, especially near the uterine cavity, where dilatation of the glands is less apparent. Isolated small decidual cells are to be seen.

Should the ovum be fertilised a decidua is produced. If this does not happen menstruation takes place.

The menstrual stage is characterised by collapse and disintegration of the superficial parts of the glands and hæmorrhage. Bits of the endometrium are torn off and a raw bleeding surface results.

During the post-menstrual stage regeneration of epithelium and stroma takes place. This is very rapid. Mitoses are found in the epithelium of the glands and not upon the surface. The latter is regenerated by gliding movements of the newly-formed

* This twisting is greatly accentuated in chronic inflammatory and hyperplastic states.

cells of the glands, possibly aided by amitotic division. Werth,[91] who examined the mucous membrane of the uterus at varying periods after curetting, tells us that mitoses are only found in the glands. The extravasated blood is quickly and completely absorbed, so that pigment is but rarely met with in the healthy endometrium.

When we compare the endometrial tumours with the uterine mucous membrane, we find that they often almost exactly correspond with it even in the finest details. This is true of the epithelium and the stroma.* The former consists of a single layer of cubical or columnar cells. They are usually non-ciliated. Cilia have, however, been recorded by many writers. They are not uncommon in extra-abdominal tumours, and have been found in intra-abdominal cases by Lauche [41] in a tumour of the intestine, and by Russel,[71] Pick,[67] Sampson,[74] and Bailey [4] in tumours of the ovaries, to mention but a few instances. It must be admitted that it is often difficult to demonstrate them in fixed tissues. They have been shown to be present in "adeno-myomata" of the uterus, and have formed one of the arguments upon which v. Recklinghausen [68] based his theory of their origin in remnants of the Wolffian body. The glands are generally easily recognisable as uterine glands. They, as well as the stroma, participate in the menstrual cycle (see Fig. 91, period of rest; Fig. 85, pre-menstrual stage; Fig. 92, menstruation). This point, emphasised more or less by nearly all writers, is particularly well brought out by Sampson [72, 73] and Lauche.[41] In specimens removed during a menstrual period, the former writer found fresh blood in the tubules and within the cavities of "tarry" cysts of the ovaries, as well as hæmorrhages into the stroma. But the reabsorption of blood is rarely as perfect in these tumours as in the uterus, since there is generally no outlet for it, and removal of insoluble blood-pigment is a slow and tedious process. The pigment, which usually contains iron, accumulates within the lumina of the tubules and in the stroma. It is either free, in the form of granules and flakes, or inclosed in large phagocytic cells (see Fig. 86).

The epithelium is said sometimes to resemble that of the Fallopian tubes (Sampson,[73] Bailey [4]) or the cervix (Sampson [73]).

It is unnecessary for our purpose to examine this fundamental identity of histological structure in greater detail. Since the endometrial tumours we are considering grow in an anomalous environment, it follows that they must be adapted to it by certain departures from the typical structure of the endometrium of the uterus. We thus find variations in the relative amount of the epithelium and the stroma, as well as differences in the shape of the tubules and the connective tissue that surrounds them.

The endometrial tissue is usually present in histological sections as more or less isolated areas. They are surrounded

* I shall refer to the characteristic cellular stroma of these tumours simply as the "stroma."

by fibrous tissue or unstriped muscle. They are generally irregular in shape, with processes that project for varying distances between the bundles of the surrounding muscle or fibrous tissue (Figs. 88, 89). They consist of cellular stroma, in which dilated lymph-spaces (Figs. 81, 90) and epithelial tubules are often present. In serial sections these processes are found either to end, or to extend between neighbouring islands of endometrial tissue, by means of which, as can often be shown, many or all of the islands inter-communicate.

The larger islands invariably contain stroma and epithelial tubules, the smaller often consist only of the former. On the other hand, naked tubules, which possess no lining of stroma and abut directly upon the neighbouring fibrous tissue or muscle, are often present. They are generally more or less cystic, and their epithelium is correspondingly flattened. It is, indeed, one of the most characteristic features of these tumours that the epithelial cells vary in height inversely with the degree of dilatation of the tubules and the amount of stroma around them. The tubules that are not dilated and that are surrounded with stroma are lined with cubical or columnar epithelium, with all the structural characters of that of the uterine mucous membrane. This is apparent in Fig. 89, a drawing of part of an endometrial tumour of the rectum. Here there are four normal cross sections of tubules, two of which are filled with recent blood-clot. On their left we see a small cystic tubule with flat epithelium and an incomplete envelope of stroma. Fig. 90, from the same specimen, shows a somewhat different, although equally characteristic state of affairs. It represents an island of endometrial tissue immediately beneath the mucous membrane of the rectum, but separated from it by the *muscularis mucosæ*. The island contains two epithelial tubules, in addition to a large and several small lymph spaces. One of the tubules is surrounded everywhere with stroma. It is slightly dilated and its contours are irregular. It is, however, lined throughout with columnar epithelium. It corresponds in structure with a uterine gland of the premenstrual stage. Immediately above it there is a large cystic tubule. Its lower part, or floor, is surrounded by cellular stroma. Here the epithelium, although not as tall as that of the first tubule, has retained a cubical or columnar shape. The upper part, or roof, of the cyst abuts directly upon the *muscularis mucosæ*, and its epithelium is quite flat. The same thing is apparent in Fig. 91, taken from a " tarry " cyst of the ovary, the main cavity of which possesses a roof lined with flat epithelium without a cloak of cellular stroma, and a floor formed of typical thick uterine mucous membrane. Here, as well as in Fig. 86, from a tumour of the inguinal canal, we have a main cavity into one side of which tubules open, themselves embedded in stroma, a structure which has aptly been compared with a " miniature uterus."

We have seen that the epithelium and stroma, which are always present, are found as more or less scattered islands. They

are therefore responsible only for part of the increase in bulk and the thickening of the affected organ. These changes are due principally to the presence of dense fibrous tissue and often of plain muscle between the islands of endometrium. Since it will be necessary to discuss these tissues later, it is enough for the present to point out that the fibrous tissue is always associated with more or less marked proliferation of the connective tissue cells of the part and with signs of a usually mild degree of inflammatory reaction. The greater part of the muscle represents the hypertrophied and proliferated musculature of the organ, which has often undergone a marked amount of interstitial fibrosis. It follows from this that its bundles are not arranged around the islands of endometrium after the manner of a *tunica propria*. In fact it is easy to see that it is these that are adapted by following the outlines of the preformed muscle bundles and by spreading between them and pushing them aside. But, as we shall see later, muscle is found in a good many endometrial tumours at various spots where it is not normally present and therefore not readily to be accounted for.

The islands of endometrial tissue attain their maximal development in the cysts of the ovaries, a part of the lining of which they form. Occasionally they attain an enormous size elsewhere, as in the cyst of the posterior wall of the pelvis described by Hartz,[30] which contained more than two litres of dark, blood-stained fluid, and was lined by a mucous membrane like that of the uterus.

The histological structure of these tumours can be briefly summarised thus: Two constituents are always present. They are the epithelial tubules and cysts, and the areas of cellular stroma. Except for certain inconstant changes of form, due to their mode of growth within the tissues of the affected part, they are identical in structure and their mutual relations with those of the physiological endometrium. This is proved by the fact that all the stages of the menstrual cycle are observed in them (see Figs. 85, 91, 92). The tubules often open into dilated cavities, which have been aptly compared with miniature uteri (Fig. 86). The endometrial tissues assume the form of islands, which can be shown in serial sections to communicate with each other. They permeate the tissues of the part implicated, and spread within pre-formed spaces between the bundles of its fibrous tissue, muscle, etc.—spaces normally occupied by blood vessels, lymphatics and nerves. The increase of bulk of the affected organ is due only in part to the presence of endometrial tissue. It depends mainly upon fibrosis, and upon hypertrophy of the pre-formed muscle. But there is occasional evidence of new formation of plain muscle, which may be the result of proliferation of its original fibres, when this tissue is present, or of its presence at an abnormal spot.

A. Endometrial Tumours of Round Ligament and Groin

Only a few instances are on record of an " adeno-myoma " of the intra-pelvic part of the *ligamentum rotundum uteri*, the great majority being situated in the inguinal region. They are generally found upon the superficial aspect of the external abdominal ring and in the *labia majora*. They, however, often extend into the inguinal canal by means of a narrow lobe or process. Leeene's [46] explanation of this is that those instances which originate within the canal are squeezed out of its narrow confines by their own increase in bulk and occupy a position outside it, or are, in rare cases, pressed back into the abdomen.

The histology of these tumours is quite typical as a rule and agrees with the general description given above. They present themselves to the naked eye as medium-sized, hard, rounded or oval masses, which are occasionally well defined and even encapsulated, but are generally more or less firmly adherent to the neighbouring fascia, abdominal muscles and subcutaneous fat. Upon section they are found to consist of firm fibrous bundles, which often radiate outwards to blend with the surrounding tissues, and inclose cysts, which vary much in size and number, and often contain blood-stained fluid. Their growth is slow. They are generally found in women between the ages of 30 and 55, but Bluhm's [7] patient was a girl of 20, and one of Emanuel's [16] a young woman of 22, whereas his other case is said to have been present for twenty years in a woman aged 31. Except in the cases of Aschoff,[3] Rosinski,[70] my previously published case,[61] Cullen's [12] second case, and one of Artusi's,[2] they are present upon the right side of the body. In Cullen's [9, 10] first case a tumour of the right groin was followed, soon after operation, by one of the opposite side.

In several cases disturbances of menstruation are noted (Cullen,[9] Szili,[85] Weishaupt,[90] Cullen,[12]) and sterility by Mahle and McCarty.[49] Increments in size and the occurrence of pain and tenderness in the tumour at the periods are mentioned by Bluhm,[7] Engelhardt,[17] and Lauche.[41] In Lauche's [41] second case small vesicles appeared upon the surface of the tumour, which was situated in Scarpa's triangle, on the day before each menstrual period. They burst upon the second day and discharged a little watery fluid or, upon occasions, a small amount of blood. The skin over the tumour was scarred. Frankl [20] records a tumour of the middle of the intra-abdominal part of the right round ligament. It was associated with a myomatous

uterus unicollis and complete absence of the left kidney and ureter. Both round ligaments were abnormally thick. The patient was a unipara aged 45. Frankl attempts to establish a causal connection between the tumour and the combined anomaly of the Wolffian and Muellerian ducts. I mention here that the only other intra-abdominal endometrial tumours of the round ligament I have seen descriptions of are those described by Cullen,[12] myself,[61] and by Artusi.[2]

Aschoff's [3] patient had worn a truss for ten years for a femoral hernia. It had to be discarded because it irritated the tumour. No hernia, however, was found at the operation. Lecene [46] and Chevassu [8] found a patent canal of Nuck to which the tumour was adherent. The latter author also found a wide canal within the round ligament, which entered the tumour. He is uncertain if it be endothelial or peritoneal. Bluhm [7] found a similar canal in the ligament. She considers it to be a lymph space.

Whereas Cullen,[9, 12] Bluhm,[7] Engelhardt,[17] Rosinski,[70] Meyer,[51] Szili,[85] Emanuel,[16] Lecene,[46] Chevassu,[8] Frankl,[20] Weishaupt,[90] the present writer,[61] and Artusi [2] tell us that the tumour was incorporated in or intimately attached to the round ligament, Aschoff [3] emphasises the fact that it was quite independent of it, and it is obvious that this was so in both cases of Lauche.[41]

Before discussing the histological peculiarities of individual cases, I will describe two additional ones which I have observed.

Case 1 (Figs. 82–84). An unmarried woman, aged 29, was admitted with a swelling of the right inguinal region, which she first noticed three weeks previously. There was no pain or discomfort. The menstrual history was not inquired into. A small right inguinal hernia was found, to the apex of the sac of which there was fixed an irregular hard tumour, which lay outside the external abdominal ring, except for a blunt process attached to the sac within the canal. It was firmly adherent to the surrounding tissues. No mention is made of the round ligament in the report.

The specimen consists of a roughly triangular hard nodule, measuring 2 cm. in its greatest diameter. It is embedded in a thick layer of areolar and adipose tissue, to which it is firmly adherent. One side of the tumour, however, bulges into a cavity, which is open above and represents the apex of the hernial sac. Upon section the tumour consists of strands of white glistening tissue, in which two small cysts and several brownish areas are present. The outlines are not well defined, since the fibrous strands radiate outwards into the fat. There is no trace of the round ligament.

Histology.—The tumour consists of irregular broad bundles of dense, but fairly cellular, fibrous tissue and unstriped muscle,

which run in all directions and are incompletely separated by bands of loose areolar tissue containing many thin-walled blood vessels, distended with blood. These strands pass into and blend with the surrounding areolar and adipose tissue, so that it is impossible to define the outlines of the tumour. Several bundles of skeletal muscle pass diagonally through the specimen, one of them at its centre between the cysts. It here pursues a straight course, uninfluenced by their presence. There are no nerves within the tumour. Where the fibro-muscular tissue is densest several islands of typical uterine mucous membrane are present. One of these is reproduced in Fig. 82. I need not waste time in describing them in detail. Hæmorrhages and big deposits of hæmosiderin are common in the cellular stroma.

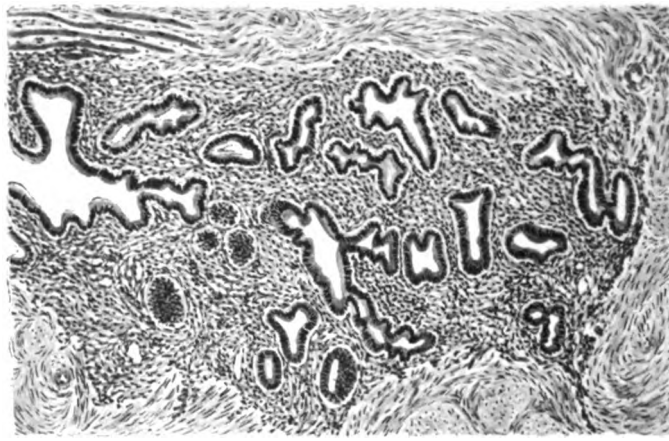

FIG. 82

Endometrical tumour of groin. Islands surrounded by involuntary muscle. A few fibres of skeletal muscle in upper left-hand corner. Magnif., 90.

The most interesting feature is a number of irregular, more or less collapsed spaces, some of which can be shown to intercommunicate or to open out of the hernial sac where it is in contact with the tumour. The wall of the sac consists of a narrow zone of dense fibrous tissue, which becomes looser as it is traced outwards, where it joins the areolar and adipose tissue on one side and the fibrous bundles of the tumour on the other. It accompanies most of the spaces given off from the hernial sac. Almost everywhere it is covered upon its internal surface by a layer of epithelial cells, which are generally flat, but often cubical and occasionally stratified. There is no doubt at all that they represent the peritoneal epithelium in a state of proliferation due to a mild degree of plastic inflammation. Where the proliferation is most intense the subjacent zone of fibrous tissue is replaced by vascular granulation tissue. But these granulations are quickly organised, and now present the appear-

ance of a vascular cellular stroma, consisting chiefly of closely packed spindle cells, identical with that of the islands of endometrium in the tumour. This resemblance is accentuated by the presence of fresh hæmorrhages and deposits of hæmosiderin,

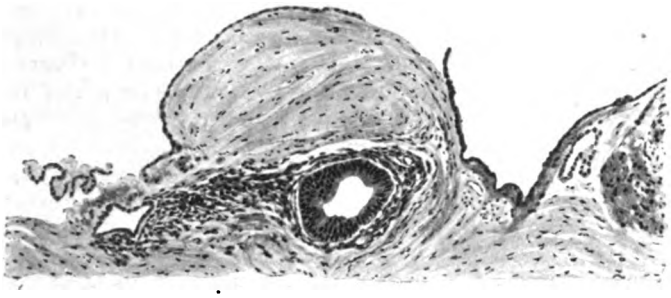

FIG. 83

Endometrial tumour of groin. Peritoneal tubules and island of endometrium. Magnif., 90.

free or within big phagocytic cells. In places like this the peritoneal epithelium is continued into the stroma as tubules lined with a single layer of flat or cubical cells. They have frequently lost their connection with the lining epithelium and form minute cysts under it. Owing to the proliferation of the

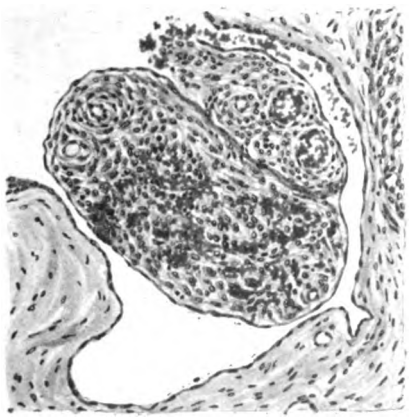

FIG. 84

Endometrial tumour of groin. Nodule of cellular stroma free within peritoneal space. Magnif., 90.

connective tissue cells these areas often project into the spaces. They frequently contain glands lined with columnar epithelium. I am, however, unable to trace these to the lining epithelium. They all end blindly. It appears as if their epithelium does not undergo differentiation into the columnar form until after separation from the surface. Fig. 83 represents a small

island of this kind, situated on the side of the hernial sac opposite that occupied by the tumour. It bears a close resemblance to an island of uterine mucous membrane.

I have said above that the nodules of vascular connective tissue often project into the peritoneal spaces. This tendency is very well marked in places, and appearances like those illustrated in Fig. 84 result. Here we see a rounded nodule of stroma lying free within a space. It is covered with a layer of flat peritoneal epithelium except above, where it is ruptured by hæmorrhage. The epithelium forms a septum across the nodule, which sub-divides it into two unequal parts. The stroma consists of round and spindle cells and capillaries. Two of these are distended with clotted blood. Extensive hæmorrhages have taken place into the stroma. The outer wall of the

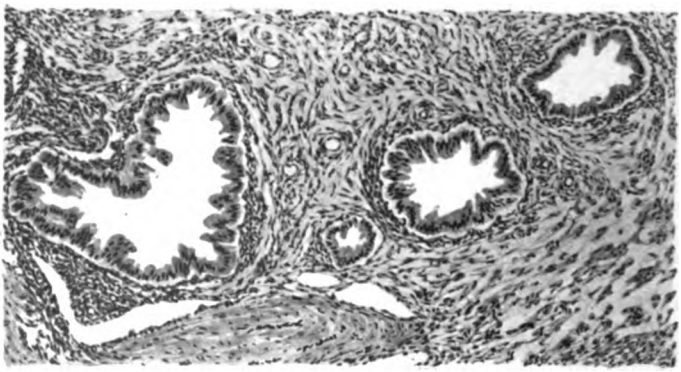

FIG. 85

Endometrial tumour of groin. Pre-menstrual stage. Magnif., 90.

space is irregular. It is lined by peritoneal epithelium, the cells of which are cubical and stratified above and on the left, and more or less flat elsewhere. Note that a narrow diverticulum is given off from the cavity, the apex of which is forked. The peritoneal space is surrounded by fibrous tissue, which separates it from cellular stroma in the upper part of the right side of the drawing. This stroma represents the edge of an island of endometrial tissue with two uterine glands. It communicates at a different level with the nodule within the space. The latter is merely a prolongation of it.

Case 2 (Figs. 85, 86).* The tumour, which was several cm. in length, was attached to the extremity of an inguinal hernia in a woman 36 years of age.

Histology.—The tumour consists of great bundles and sheets of fibrous tissue, which run in all directions and pass outwards to be lost in the areolar tissue and fat at its periphery. There is no unstriped muscle in the tumour itself, but a few small bundles

* I am indebted to Mr. E. W. Bowel for the opportunity to examine sections of this case and for permission to use it

of it are found adherent to one of its poles. A good many fibres of skeletal muscle are present in its superficial parts. Some of these extend into the substance of the tumour, and are often surrounded by the islands of endometrial tissue. These are large and consist of typical uterine stroma, with recent hæmorrhages and deposits of hæmosiderin. They are often wrapped about small arteries and nerves, even near the centre of the tumour. The uterine tubules are numerous and correspond with the pre-menstrual stage. Fig. 85 shows that they are dilated and that their epithelium has begun to proliferate and be desquamated. It also demonstrates the pre-menstrual loosening of the stroma due to accumulation of œdema fluid. Many tubules open into cysts (Fig. 86). These are occupied by recent and old hæmorr-

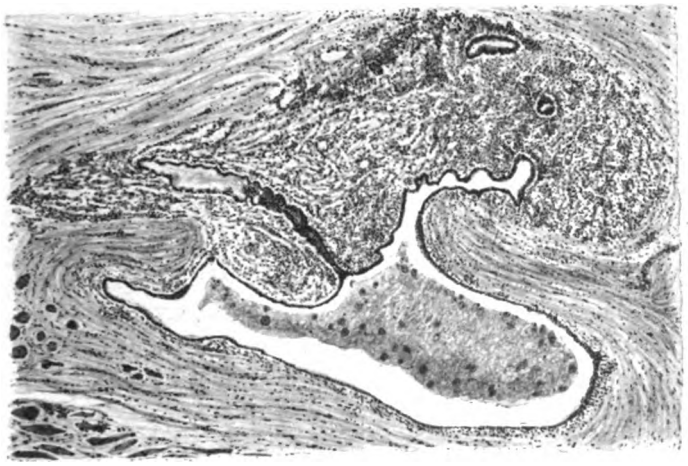

FIG. 86

Endometrial tumour of groin. Miniature uterus. Fibres of skeletal muscle in lower left-hand corner. Magnif., 50.

hages and contain numbers of large pigment cells. Very striking "miniature uteri" result. There are no traces of the hernial sac in the sections.

We can summarise these facts thus :

(1) We have seen that these tumours are identical in the essential *minutiæ* of structure and the function of menstruation with the physiological endometrium. Uterine tubules are present as well as the characteristic stroma. The former are often cystic. Both constituents contain blood and hæmosiderin as a result of former menstrual activity. Nothing could be more characteristic of the pre-menstrual stage than Fig. 85. I have not been able to demonstrate the presence of cilia in either of my specimens, but they have been seen by Aschoff [3] (doubtfully), Engelhardt,[17] Meyer,[51] Chevassu,[8] Frankl.[20]

(2) Whereas the majority of these tumours are incorporated in the round ligament and have originated within it, a few cases remain in which these relations were not established. They are those of Aschoff,[3] Lauche,[41] and the two described in this paper. There was no plain muscle present in my second case, except for a few bundles attached to one end of it. It is impossible to be certain of their origin, but they resemble the muscle of the round ligament, and this is their most obvious source. My first case contains a good deal of this tissue, in spite of the fact that it was apparently not connected with the ligament. But it may well have been separated from this structure by the growing tumour and incorporated with its other tissues to form a part of its structure. Even when the tumour is definitely included in the ligament it occasionally contains no plain muscle (Szili,[85] Nicholson,[61] Artusi [2]), and we shall see later that this tissue is sometimes present in corresponding tumours of the umbilicus, laparotomy scars, and ovaries.

(3) Fibres of skeletal muscle are present in the substance of the tumours described by Bluhm,[7], Weishaupt,[90] and in my cases. They, and the nerves in my second specimen, present no signs of active proliferation. They are merely passively surrounded and included by the growth of the fibrous tissue. In my cases the muscle is certainly derived from the neighbouring abdominal muscles, to which the tumour was adherent. Another possible source for it is the fibres of striped muscle found in the round ligament and corresponding with the cremaster of the male sex. In no sense of the word are these fibres to be regarded as intrinsic components of the tumours.

(4) The fibrous tissue which forms the greater part of the mesenchymal parenchyma of the tumours is dense and varies considerably in its cellularity. Its edges are indistinct and fuse with the surrounding subcutaneous and fascial tissues. It follows from this that a capsule is entirely wanting in my specimens. Again, there are many signs of a slight amount of infiltration with leucocytes and of recent progressive fibrosis. The blood vessels are numerous. In places they are young and full of blood, in others they are thickened and sclerosed. All these appearances indicate that they are produced by *a reaction of the connective tissue of the part* in which the tumour has developed. To apply the word " inflammatory " to this reaction does not, perhaps, define it properly. But it is clearly a plastic fibrosis, a reaction to a mild form of irritation, which may well have been induced by the " foreign body " action, or pressure and growth, of the ectopic endometrial tissues in the areolar tissue of the groin or round ligament. I conclude that the fibrous

tissue is not an essential part of the tumour; it merely assists in its production. Although it is often well enough defined for the naked eye, the microscope shows that these tumours are not fibro-adenomata, to say nothing of adeno-myomata, in the generally accepted sense of the term. I conclude that *the endometrial tissues are the only essential constituents of these tumours.*

(5) The specimen described by me [61] a few years ago and those of Artusi [2] are peculiar in many respects. They are intra-abdominal and situated at the centre of the round ligament, close to its attachment to the uterus. In my case the stump of the ligament was thickened and puckered. In the first of Artusi's

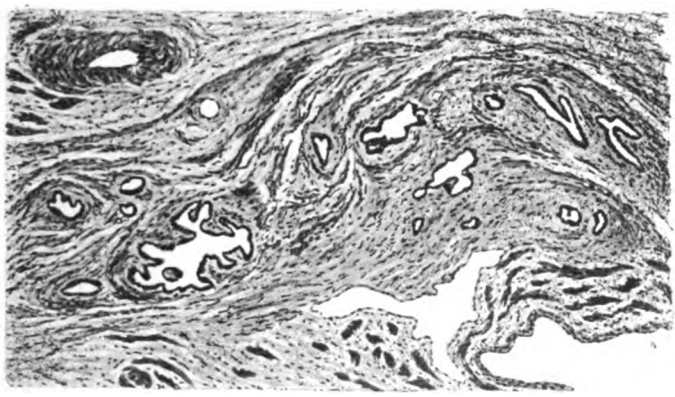

FIG. 87.

Atrophic endometrium in proximal end of round ligament. Magnif., 90.

cases it was thickened as a whole and presented an almost imperceptible swelling at the site of the tumour. Fig. 87 reproduces the histological structure. There are a few more or less dilated small tubules lined with atrophic epithelial cells and embedded in cellular fibrillar stroma, which bears no resemblance to that of the endometrium. We both interpreted them as Wolffian tubules, about which I shall say more directly. But Lauche [43] suggests that, since Artusi's cases occurred in old women—an argument which is equally cogent in my case—they may well be the atrophied remains of endometrial tumours which have undergone involution and atrophy since the menopause. Although the structures in question are central and unconnected with the peritoneum, and there was no apparent pathological anomaly in Artusi's cases, the ligament in mine was distinctly deformed and scarred. This suggests a connection with the peritoneum at an earlier date.

(6) The presence of dilated and branched cavities, interpreted as lymph spaces, in the substance of the tumour is noted by Engelhardt,[17] Rosinski,[70] Szili,[85] and Emanuel.[16] In the two latter cases a large central cyst was present, interpreted as a lymph cyst. Bluhm [7] and Chevassu [8] found a dilated space at the centre of the round ligament. It enters the tumour. My first case contains many irregular peritoneal spaces which correspond with descriptions of some of these. I suggest that some at least of the recorded spaces are likewise of peritoneal origin.

(7) We have seen that Aschoff's [3] patient had worn a truss for a femoral hernia for ten years, which was discarded soon after the tumour made its appearance. No hernia was, however, found at the operation. Lecene's [46] tumour was attached to a peritoneal diverticulum, which represented the internal opening of the inguinal canal. In Chevassu's [8] case the round ligament was surrounded by a peritoneal sac, the canal of Nuck, which accompanied it into the substance of the tumour. In both my cases the tumour was adherent to the sac of an inguinal hernia. We have clear evidence of a connection with a process of the peritoneum.

This evidence is strengthened when we examine the histological structure of Chevassu's and my first case. In the former tubules were traced from the apex of the peritoneal diverticulum into the tumour, and in the latter islands of endometrium were found immediately under the epithelium of the peritoneal spaces of the hernial sac (Fig. 83), between it and the tumour proper. The latter was ill defined and had apparently increased in size by appositional growth or gradual inclusion of outlying islands of endometrium by fibrosis around them, much in the same way as I have described in a fibro-adenoma mammæ in Study VIII. Some of these islands contain peritoneal tubules and cysts lined with an epithelium which is identical with that of the superjacent peritoneal space. They often contain uterine tubules as well. Although I could not demonstrate direct continuity between these two kinds of tubules, it is obvious that it must have existed at one time. The only alternative is to assume that the "uterine" tubules were pre-formed and that they had induced proliferation of the peritoneal epithelium and formation of cellular stroma. But then, why should they always be present immediately beneath the peritoneum and not in more remote situations?

These two cases together produce good evidence of anatomical continuity between the peritoneal epithelium and that of the tumour. Those of Aschoff [3] and Lecene [46] suggest that it may

have been present at an earlier date. If the spaces and cysts discussed in Par. 6 are derivatives of the cœlom, they give additional support to this view.

(8) I take this opportunity to discuss a question of histiogenesis, although I anticipate by doing so. One of my excuses for these studies is that in them I attempt to show the total inadequacy of dysontogenetic theories of tumour formation. It is still the fashion to find an easy " explanation " in congenital anomalies, and more particularly in displaced cell-rests, as a cloak for ignorance and to " increase vanity." It is therefore only natural that the Wolffian body, the fetish of pathologists, should be invoked in endometrial tumours in general and those of the groin in particular. It so happens that this view appears to be supported by the latter, whereas it is a pure article of faith, or superstition, in most of the other situations in which these tumours are found.

Chevassu [8] describes what he took to be a Wolffian glomerulus in his specimen, and I see that an authority like Meyer [58] agrees with this interpretation. I am at a disadvantage in not having seen Chevassu's sections, but, if it be permissible to form an opinion from his description, I am unconvinced. I admit that the structure figured by him bears a close resemblance to an immature glomerulus, that it is very regular in shape, that it fills its " Bowman's capsule " almost completely, and that it corresponds very well in size with a mesonephric glomerulus. Both it and its " capsule " are covered by a very regular layer of flat epithelioid cells. But the round cells of its stroma bear a very close resemblance indeed to the wandering cells (lymphocytes or plasma cells) which are present at its periphery, and the capillaries are relatively few in number and certainly do not form the bulk of the glomerulus. There is nothing to distinguish the flat endothelioid lining cells from lymphatic endothelium or cœlomic epithelium. The complete absence of septa in the glomerulus is explained by Chevassu on the assumption that it is immature, but it can be equally well explained by assuming that it is not a true glomerulus at all. And were it an immature glomerulus, ought not the epithelium on its surface to be cubical instead of flat? The bay or " excretory duct," lined with cubical epithelium, is wonderfully like many of the peritoneal spaces in my first specimen. These appearances led Chevassu to believe that he had found an immature *metanephric* glomerulus. But he altered his opinion in favour of a *mesonephric* glomerulus because of the presence of a narrow finger-like diverticulum of the outer wall of " Bowman's capsule," which he tells us is characteristic of the mesonephric glomeruli of Selachians.

I cannot accept this argument. I have, in a former paper,[63] protested against the abuse of the methods of comparative anatomy that is practised by pathologists and need not repeat my arguments here. I am, however, glad to see that Lauche [44] has come to very much the same conclusions. I do not know, nor do I care very much, if man is descended from fish-like animals which corresponded more or less closely with the present-day Selachians. But until good evidence is produced for the assumption that the "Bowman's capsules" of these animals actually possessed these finger-like diverticula, I shall regard Chevassu's and similar speculations as wild flights of an exuberant imagination.

I have reproduced, in Fig. 84, a structure that I believe to be of the same nature as Chevassu's "mesonephric glomerulus." I admit that it is very much larger and more irregular in shape, and that the space into which it projects is enormously bigger. But the nodule is covered everywhere with flat epithelium, except at its upper pole, where a hæmorrhage has taken place. "Bowman's capsule" is lined with cubical epithelium where it is widened. No matter that it is stratified. The structure in question is merely an invagination of vascular cellular stroma into an irregular peritoneal sinus. Similar things are described by Schindler [77] and Kitai [39] in tarry cysts of the ovaries. I can see no reason why Chevassu's "glomerulus" should not represent a similar invagination, especially since a finger-like process extends outwards from "Bowman's capsule" in Fig. 84. This has, of course, nothing to do with Selachians, extinct or recent, but is simply a narrow bay given off from an irregular branched peritoneal recess. Similarly, the glomeruli described by Cullen [9] and others appear to me not to be related to true glomeruli. Even Bluhm,[7] who explained her tumour as of Wolffian origin, points out that the "glomerulus" figured by Cullen is larger with a magnification of only sixteen diameters than those of v. Recklinghausen [68] with one of two hundred. Cullen informs us that some of these bodies contain tubules in their stroma. This should be evidence enough that they are no more than "pseudo"-glomeruli. These arguments apply to the "ampullæ," and indeed to all the segments of "mesonephric tubules" described by v. Recklinghausen, but I cannot afford the space to apply them here.

I have discussed these "glomeruli" at length since, should they be true glomeruli, they definitely establish Chevassu's [8] thesis that we can assert positively that the tumours containing them are of Wolffian origin. I submit that neither Chevassu nor anyone else has as yet produced the necessary proof. There

is no definite *histological* evidence that the endometrial tumours of the round ligament and groin are derivatives of displaced Wolffian tubules.

Meyer [58] at the present time does not doubt that the great majority of these tumours have nothing to do with the mesonephros. He regards them as derivatives of the peritoneal epithelium. And I have not the slightest desire to deny the *possibility* of their origin in mesonephric tubules. I am at pains in Study V to show that tumours do occasionally arise in displaced tissues or embryonic cell-rests, but I insist that the latter are not *predisposed* in the very slightest degree for tumour formation. Then why attempt to deny the potentiality for tumour formation to the epithelium of the Wolffian body? Far be this from me. But I maintain that two things are necessary and a third desirable for a supposition of this kind to be more than a speculation. Firstly, we must demonstrate a path by which mesonephric cells can reach the region occupied by the tumour we wish to explain by their aid. Secondly, we must prove that these remnants are actually present, at all events in the embryo, and have therefore reached the area. Lastly, we strengthen our case when we show that they have been found to persist *in situ*, even though it be in the differentiated state. Since no endometrial tumour has been described in a child, this should be until the age of puberty at least.

It is generally stated that a mechanism suitable for the conveyance of Wolffian epithelium into the inguinal region is furnished by the inguinal fold, or *plica gubernatrix*, which is attached to the lower pole of the Wolffian body and in which the round ligament is developed. It increases in length because this organ gradually rises cephalad during development, as well as on account of the general increase in size of this region. It is assumed that, should a tubule project slightly above the surface of the Wolffian body, it is inclosed in the fold and separated from it. But Meyer,[57] to whom we owe most of our knowledge of the so-called embryonic displacements, and who has shown quite conclusively that many of them are no less than physical impossibilities,[54,56] points out that the distance between the caudal end of the Wolffian body and the lateral abdominal wall, where the inguinal canal is developed, is much too great at every stage of embryonic life for it to be possible for Wolffian "rests" to reach the insertion of the round ligament into the subcutaneous tissue. But at an early stage of development the caudal end of the primitive ureter, closely invested by the cap of metanephrogenic blastema, lies under the ectoderm of the future inguinal region. It is thus possible for cells of this blastema to

remain behind at this spot after the subsequent displacement of the ureter and its cap in the dorsal direction by the intercalation of newly-formed layers of tissue between it and the lateral abdominal wall. If tubules are found in the groin, they must belong to the *meta-* and not the *meso-nephros*.

Forrsner,[18] the most recent investigator of the subject, criticises Meyer's [57] conclusions. He denounces attempts at the localisation of a blastema which has not even begun to undergo differentiation as little short of speculations. They certainly possess no claim to be considered established facts. The kidneys are placed much too far dorsally for parts of them to be included in the inguinal region. He points out that Meyer has restricted his observations to the ventral tubules of the mesonephros, which follow the course of the Wolffian duct, and shows that there exist in addition certain tubules placed dorsally near the caudal pole of the organ. He describes and figures these in the mesenchyme of the abdominal wall a considerable distance dorsally and caudally from the boundaries of the Wolffian body. Although it is impossible to localise the future inguinal region accurately at this stage, these tubules extend quite far enough caudad to occupy it eventually.

There appears, therefore, to be no difficulty in accounting for the possibility of the presence of mesonephric tubules in the groin. They are not dragged downwards by the round ligament in its development. They are therefore not the result of *displacement* but of *persistence*. In this respect they agree with our knowledge of ectopic cell-rests in general.

Meyer [57] and Forrsner [18] have actually demonstrated the presence of aberrant tubules in this region. Meyer, in an otherwise normal female human embryo of 23 mm., found an S-shaped tubule with a rudimentary glomerulus in the sub-peritoneal tissue upon the right side of the pelvic wall, slightly caudad to the insertion of the round ligament into the abdominal wall and to the lower pole of the Wolffian body. He points out that this tubule, which he believes to be metanephric (*v. supra*), might easily be drawn into the inguinal canal at the formation of the *processus vaginalis peritonæi*, and thus reach the region of the external attachment of the round ligament. Forrsner found several inter-communicating tubules and a glomerulus in the right inguinal region of a human embryo of 10 cm. They occupy a position dorsal and lateral to the inguinal ligament. He is unable to say if they be meso- or meta-nephric from their structure, but is induced, by the theoretical reasons referred to in preceding paragraphs, to accept the former alternative.

The first two of our postulates are thus satisfied : It is possible

for Wolffian tubules to occupy the inguinal region and they have actually been demonstrated upon two occasions in embryos. But it is a far cry from the 10 cm. embryo to the girl at the age of puberty. This gap has, to the best of my knowledge, never been bridged. It is but fair to add that I know of no investigations which attempt to do so. In default of evidence we must ask if it is at all likely that Wolffian tubules should persist indefinitely. That they do so in the undifferentiated state can be excluded upon the analogy of the behaviour of the cell-rests we have examined in earlier studies. We have seen that rests are met with in various parts of the body in a state of differentiation, and we must now inquire into the normal behaviour of persistent remnants of the Wolffian body and draw our inferences therefrom. We admit at once that certain of its tubules persist normally, but only at one or two definite spots, the hilum of the ovary and the broad ligament. They disappear elsewhere. Forrsner [18] mentions again and again that they are undergoing necrosis in the embryos examined by him. The chances of their presence in the inguinal region at the age of puberty are extremely remote, although it is within the bounds of possibility for them to survive.

This possibility admitted, we have yet to ask ourselves if there are sound reasons for the assumption that endometrial tumours originate in the cell-rests which have been demonstrated or may be assumed to be present at the same spot. I submit that further evidence is necessary. The tumours must correspond in histological structure or in one or other physiological character with the differentiated organ from the undifferentiated protophase of which they were displaced or with the tumours that commonly arise in it. We have seen, in Study III, that the presence of nodules of suprarenal cortex in the kidneys is an established fact of frequent occurrence. In Study VI we have seen that the commonest tumours of these organs, the so-called hypernephromata, bear a close structural resemblance to them. But we came at the conclusion that this resemblance is deceptive, and that no instance has been described in the kidneys, the origin of which in an accessory suprarenal is assured upon histological or physiological evidence. But to return to the endometrial tumours. Pick [65] has recorded an interesting case in which the site of the left epoöphoron was occupied by a tumour which agrees perfectly, in its ampullæ, pseudo-glomeruli, etc., with those assumed by v. Recklinghausen [68] to be of mesonephric origin. The right epoöphoron was replaced by a tumour with the typical structure of the uterine mucosa. Pick has established a topographical relation between a normally

persistent rudimentary survivor of embryonic life and an endometrial tumour, but, in my judgment, not an histiogenetic one with any degree of certainty. But his conclusion that all "adeno-myomata," or, at all events, those outside the uterus, are therefore derived from remnants of the Wolffian body is, to say the least of it, illogical.

I agree with Meyer [53] that too much importance must not be attached to histological structure, since it is apt to deceive, but I think he goes too far when he denies it importance of every kind. The tubules of the epoöphoron in the adult female (see Fig. 18 (II)) possess no very characteristic structure. They are, however, not surrounded by "uterine" stroma. To argue that, because endometrial tumours, like that of Pick,[65] at the site of the epoöphoron, possess this stroma, Wolffian tubules acquire it if they undergo proliferation and tumour formation, is surely an argument in a vicious circle. The only epithelium in the normal body which rests upon this stroma is the uterine epithelium. We ought therefore to say that the epithelium with which it is associated in pathological lesions is uterine. And this we ought to do without prejudice for the question whether it was or was not Wolffian originally and had later changed its type. These changes of type are common enough, as we have seen when we investigated the heteromorphoses.[62] Again, why should these tumours, if they arise in mesonephric epithelium, assume the structure and functions of the endometrium, since the Wolffian body is related only to Mueller's duct in that both are derivatives of the cœlomic mesoderm? Why do not the kidneys, which are developed in what is practically the same blastema as that of the Wolffian body, produce endometrial tumours?

If the epithelium of the Wolffian body undergoes heterotopic differentiation into uterine glands as postulated by v. Recklinghausen,[63] Pick,[65, 66] and all the supporters of the theory of the mesonephric origin of endometrial tumours, why should not the peritoneum, the direct representative of the cœlom, and not merely one of its descendants, possess this potentiality to a greater extent? All these writers forget that it is not the natural fate of Wolffian epithelium, when it persists into adult life, to be converted into uterine mucosa, as shown by the structure of the epoöphoron, any more than it is that of the peritoneum. An additional pathological or abnormal stimulus is required for the change to take place.

Since, therefore, every argument in favour of the origin of these tumours in remnants of the Wolffian body can be made to apply with even greater force to the peritoneum, I conclude that

there is no evidence, and but little likelihood upon theoretical grounds, that the endometrial tumours of the inguinal region and round ligament in particular and these tumours in general originate in mesonephric epithelium. The only tumour that I know of for which this origin is assured is that attached by a stalk at the junction of the uterus and the Fallopian tube described by Meyer,[53] but its histological structure differs *toto cœlo* from that of endometrial tumours.

B. Endometrical Tumours of Umbilicus

Among the tumours of the umbilicus, many of which can be traced to anomalies of development, there is a class which was defined by Mintz [59, 60] as the "true umbilical adenoma," and the close histological and physiological agreement of which with the uterine mucosa was realised first by Goddard [25] and later Cullen.[11]

These tumours are again only found in adult women, the youngest of whom was 27 and the oldest 57 in the cases I have read. They had been observed by the patient for varying periods from two months to twenty-seven years (Edwards and Spencer [14]), but most of them gave at least one year's history. In the cases of Mintz,[60] Herzenberg [31] and Ehrlich [15] the tumour, which occupied its typical site in the umbilical depression, was associated with, but apparently independent of a laparotomy scar. Most writers mention that their specimens increased in size, darkened in colour, and gave rise to pain and tenderness at the menstrual periods. The discharge of blood-stained fluid at these times is noted by Green,[26] Mintz,[59] Goddard,[25] Zitronblatt,[92] Mahle and McCarty,[49] Edwards and Spencer,[14] and Keitler.[38] The first and last mentioned of these authors found one or more sinuses through which it had taken place. The presence of menstrual disturbances is occasionally referred to.

The naked-eye appearances are characteristic. The tumour occupies the umbilical scar, through which it projects as a rounded and even, though occasionally papillomatous (Goddard [25]) nodule, which is covered by deeply pigmented and discoloured skin, to which it is often firmly adherent. It rarely exceeds a diameter of 4 or 5 cm. A section reveals bundles of fibrous tissue, between which small cysts and brownish areas are often visible. The dense fibrous tissue resembles scar tissue. It occupies the subcutaneous fat. Its edges are usually ill defined and blend with the cutis and even the abdominal muscles. The peritoneum was involved in the

cases of Giannettasio,[24] Barker,[5] one of Mintz'[60] later cases and that of Herzenberg[31] in which the tumour adhered to the omentum, and in Waegeler's[89] case, where a pedicle extended between the tumour and the peritoneum. Tobler[87] records a deep funnel-shaped diverticulum of the peritoneum, to which the tumour was attached. An umbilical hernia was present in the cases of Mintz,[59] Mahle and McCarty,[49] who note that the tumour was not connected with it, and in one of Lauche's[41] cases. Green,[26] Goddard,[25] Zitronblatt,[92] Keitler,[38] and Schiffmann and Seyfert[76] describe the peritoneum as normal.

The histological structure of these tumours of the umbilicus corresponds with that of endometrial tumours elsewhere. There are tubules and cysts, isolated and in groups, lined with a single layer of flat, cubical, or columnar epithelium, which varies in height in accordance with the degree of dilatation and with the amount of the surrounding cellular stroma. This is typically "uterine" in structure. Schiffmann and Seyfert[76] describe areas of decidua, the cells at the edges of which gradually pass into the ordinary stroma. Their patient was aged 57. Her only pregnancy had taken place thirty years previously. They definitely exclude a recent pregnancy, but the menopause had apparently not been reached. Unstriped muscle was found in greater or lesser abundance by Green,[26] Mintz,[59] Goddard,[25] Barker[5] (see Cullen[11]), Cullen,[11, 12] Matthias,[50] Edwards and Spencer,[14] and presumably by Mahle and McCarty,[49] since they describe their specimen as an adeno-myoma. Ehrlich,[15] Lauche,[41, 42] Tobler,[87] Keitler,[38] and Schiffmann and Seyfert[76] were unable to find this tissue, as they take care to state. Practically all the instances recorded contained blood and hæmatogenous pigment in the tubules and stroma.

We see that these tumours contain islands of functioning uterine mucous membrane. Cullen[11] deserves the credit of having been the first to convince others of this fact in his monumental work on "The Umbilicus," although it had been clearly recognised and stated by Goddard.[25] It was Lauche[41] who established the identity of these umbilical tumours and the endometrial tumours in other situations.

Nearly all the older writers brought these tumours into relationship with remnants of the vitelline duct, which frequently persist as polypi and cysts in the umbilical region, even when they realised their striking similarity to the uterine mucosa. But these vestiges are always lined with alimentary epithelium, the structure of which is that of the stomach or intestine (see[63]). Even the most rudimentary of them contain

many goblets,* and a cuticular border can be seen in many of their cells. Without entering deeply into the structure of these malformations, we can dismiss them by saying that they are always endodermal in type and not mesodermal, like the endometrial tumours, nor are they associated with "uterine" stroma or with recurrent hæmorrhages at the menstrual periods.

Since the epithelium of the bladder often undergoes metaplasia into mucus secreting glands, *e.g.* in *cystitis cystica* (Stoerk [83]), the suggestion has been made that our umbilical tumours are developed in remnants of the urachus. But this structure, like the vitelline duct, is endodermal. It is a well-known fact that the endodermal part of the bladder has the same structure as its mesodermal trigone and the ureters. Since the trigone is the representative of the Wolffian duct and the ureters are diverticula of it, and since the duct is ultimately derived from the cœlom, and the Wolffian body, which, as we have seen, is assumed to be the starting-point of adeno-myomata, is also one of its derivatives, it has been argued that these umbilical tumours represent persistent parts of the Wolffian body or duct.† But apart from the fact that it is impossible to account for "displacements" of these organs into the umbilicus, except perhaps in malformations of the very gravest and grossest kind, which would certainly all be non-viable, I must reiterate that theories of this sort apply to the peritoneum with much greater force than to its collateral relations.

We have seen that the tumour was associated with an umbilical hernia in four cases, that it implicated the peritoneum five times, being adherent to the omentum twice (Mintz,[60] Herzenberg [31]), and that it was joined with the peritoneum by a band in the case of Waegeler [89] and united with a peritoneal diverticulum in that of Tobler.[87] This writer has examined the site of attachment with the microscope. He finds that the peritoneal epithelium is cubical and that tubular glands extend from it into the tumour almost as far as the skin. It is, indeed, these structures which form the epithelial

* Goblet cells have been described in the epithelium of the uterus (Schridde [78]) and I have seen them here. But they are rare and few in number and by no means characteristic of this organ. They do not, therefore, form a sound basis for comparison and arguments anent histiogenesis.

† A round-about argument surely, but one the many layers of which form a warm cloak for ignorance.—I may be accused, especially by German pathologists, should any of them read this paper, of wasting time in struggling with the Wolffian body in the Year of Grace 1926. My apology is that morbid histology is still in its infancy in this country when compared with the Continent. Many superstitions, which have died a natural death elsewhere, still await dispersal in the light of knowledge here.

elements of the tumour and are surrounded by "uterine" stroma. Cullen [11] has described the relations and fate of the exocœlom of the embryo and shown that more or less pronounced diverticular depressions or "peri-umbilical fossettes" of the peritoneum are by no means uncommon in adults. They are to be regarded as persistent parts of the exocœlom. Lauche [41] attempts to correlate them with the endometrial tumours of the umbilicus, which he thus regards as derivatives of the peritoneum. We have seen that a definite anatomical continuity between the epithelium and the peritoneum has been established in a few tumours of the inguinal region, and this is also true of Tobler's [87] tumour of the umbilicus. I shall revert to this question later.

Cilia are figured on the epithelium of a tumour of the umbilicus by Giannettasio,[24] and described by Goddard,[25] Mintz,[60] Herzenberg,[31] Waegeler,[89] Cullen,[11] Lauche,[41] Tobler,[87] Keitler,[38] and Schiffmann and Seyfert.[76] Their presence proves nothing more than that the epithelium is uterine in type. It accentuates the improbability of an endodermal origin in a remnant of Meckel's diverticulum, since the only part of the alimentary canal that is lined by ciliated epithelium in development is the œsophagus (Schridde [78]), and this organ does not contain "uterine" stroma at this or any other stage.

v. Noorden [64] saw many hypertrophied sweat glands in and around his umbilical tumour. I only mention his belief that it had originated in them because Schiffmann and Seyfert [76] have lately used this association as an argument in favour of a congenital dyscrasia of a general and undefined sort, upon the analogy of hypermastia and the hypernephromata.

C. Endometrial Tumours of Laparotomy Scars

These tumours differ from those we have considered hitherto in that they are recorded from a comparatively wide area, where they are always developed in a laparotomy scar. Their site depends upon that of the original incision, and they are thus difficult to explain on the assumption of the presence of persistent embryonic cell-rests. On the other hand, they appear at first sight to establish the view that endometrial tumours, or at least those found within the abdomen, are the result of implantation of uterine mucous membrane. Since this is a question of considerable histiogenetic importance, I propose to give brief abstracts of the recorded cases before describing the one I have examined.

Meyer [52] describes the first case in a woman aged 35, who had been operated two years previously for ventri-fixation of the uterus and removal of the right adnexa. A painful nodule developed in the scar below the umbilicus. Excision of scar. Fundus uteri firmly attached to tumour and omentum adherent between uterus and abdominal wall. Removal of tumour together with attached part of fundus and omentum. Fundus found to be attached to abdominal wall by a " mesentery " about 5 mm. in length. *Histology:* Skin atrophic without cutaneous appendages. Tumour consists of dense scar tissue with tubules and cysts and cellular stroma. Hæmorrhages and blood pigment. Only one cyst extends for short distance into " mesentery." Near here there is a " silkworm " thread, surrounded by cysts, tubules, and cellular stroma. No epithelial elements in excised part of uterus or omentum. —Klages' [40] case concerns a middle-aged woman who had been operated six years previously for ventri-fixation of the uterus and removal of the right adnexa and the vermiform appendix. A tumour made its appearance in the lower part of the scar four years later. It assumed a red colour and became very painful at the menstrual periods. Scar ascends in linea alba for 10 cm. above pubes. Its lower end contains a reddish, firm, tender nodule, of about the size of a walnut, and raised slightly above level of surrounding skin. Excision : Tumour produced into a stalk, which traverses peritoneal cavity and is attached to anterior wall of uterus and adherent to a tag of omentum. *Histology:* Radiating bands of dense fibrous tissue. Narrow bundles of plain muscle, most numerous at base of tumour. Large and small cysts and tubules, partly surrounded by inflammatory granulation tissue and partly by cellular stroma. Hæmorrhages.—v. Franque [21] examined a V-para aged 39, upon whom a laparotomy had been performed four years previously for suture of a perforation of the uterus after an abortion. A short time later a tumour was noticed in the lower part of the scar, which attained the size of a walnut during the last six months. Excision : Tumour only slightly movable, covered by pigmented skin. Inclosed in subcutaneous fat, but produced inwards for a distance of about 3 cm. as a wedge-shaped cicatricial mass, which contains punctate black and yellow areas. Not connected with peritoneum. *Histology:* Tubules and cysts. Cilia and goblet-cells. Cellular stroma. Hæmorrhages and pigment.—Fraas [19] saw a woman, aged 45, in whom ventri-fixation of the uterus had been performed twenty years previously. Scar on left of middle line, 5 cm. in length, retracted. Its lower end very firm. Excision of scar, which is firmly adherent to the fundus of the greatly elongated uterus by means of dense scar tissue. Hysterectomy. *Histology:* Dense scar tissue containing cysts and " uterine " glands. These are present only in scar and adherent parts of surface of uterus, whereas they are absent in the myometrium and are therefore independent of the endometrium. No adeno-

metritis of the uterus.—Cullen [12] describes an adeno-myoma of the rectus muscle. A laparotomy had been performed on the patient, a woman aged 34, nine years previously for rupture of the uterus following an abortion. A year later she gave birth to a full-term child. Menstruation normal. A few days before admission she noticed a small tender nodule in the rectus abdominis muscle, on the left of the middle line, under the lower end of the scar, but not attached to it. Operation: Tumour, 3 cm. in length, excised. Firm and fibrous, mottled, unencapsulated. *Histology:* Unstriped muscle with areas of typical uterine mucous membrane. Blood and pigment.—Mahle and McCarty [49] describe three cases. (1) Woman aged 30, with a small tumour of the lower end of a laparotomy scar of two years' duration. Painful at periods. Operation: Tumour attached to left Fallopian tube about four cm. from uterine horn. *Histology:* Adeno-myoma. (2) IX-para, aged 46. Last pregnancy ten years ago. Ventri-fixatio uteri several years ago. Tumour present in scar for about a year. Painful at periods. Operation: Tumour situated in abdominal wall above symphysis pubis, 8 cm. in diameter, firmly attached to right side of uterus. Since it infiltrated the retro-peritoneal tissues and was apparently inoperable, only a piece was excised for histological examination. Tumour firm, with pigmented glandular and cystic areas. *Histology:* Adeno-myoma. (3) This specimen is described by these authors as a tumour of the groin together with that referred to in section A. It clearly belongs to the group now under discussion. An unmarried woman, aged 50, in whom an appendicular abscess had been drained twenty-five years previously. Two small nodules appeared in the scar four years before admission. They were painful at the periods. Excision: The tumour occupied the scar and extended downwards to the femoral ring. An inguinal hernia and fibroids of the uterus were present. *Histology:* Adeno-myoma.—Lauche [41] collected four cases. (1) Unipara, aged 30. Laparotomy for double pyosalpinx and ventri-fixation of uterus of four years' standing. Soon after she noticed a thickening of the lower end of the scar. Vesicles appeared here at the menstrual periods. Latterly they have discharged blood-stained fluid at these times. Operation: Tumour, which contains many isolated cysts, extends as far as peritoneum, but not beyond it. No direct connection with uterus. *Histology:* Dense bundles of scar tissue. Branched tubules and cysts with cellular stroma. Blood and pigment. Areas of round-celled infiltration. Bundles of twisted and knotted fibres of unstriped muscle. Peritoneum not present in sections. (2) Age 35. Only pregnancy eleven years previously. Ventri-fixation of uterus two years before admission. Right adnexa found to be adherent to uterus. Cystic left ovary removed. Periods painful since then. A tumour made its appearance in the scar. It increased in size at the periods. Excised together with piece of peritoneum. Structure of

abdominal wall obliterated, replaced with scar tissue with brownish cysts. Tumour connected with fundus uteri, a part of the surface of which was excised. *Histology:* Same as that of first case, except for absence of unstriped muscle. (3) Age 37. Several abortions. Operation on ovaries thirteen years previously. Since then three normal pregnancies, the last four years ago. For past six years pain in scar and dysmenorrhœa. Operation: Excision of thickened lower end of laparotomy scar, which contains blood-stained cysts. Peritoneum opened. Dense adhesions between stump of left adnexa, removed at first operation, and scar. *Histology:* See first case. No unstriped muscle present. (4) Unmarried woman aged 26. Periods always irregular. Laparotomy for tumour of ovary and ventri-fixatio uteri four years ago. Tumour of lower end of scar for six months. Painful and enlarged at periods. Operation: Tumour under abdominal fascia. Not connected with peritoneum, which was not opened. Uterus adherent to abdominal wall. *Histology:* Similar to that of first case. Small round isolated areas of unstriped muscle.—Tobler [87] records five cases. Four of them concern women aged 22, 25, 41, and 32 respectively, two of whom had undergone tubal sterilisation two years previously, and a third a laparotomy for a tubal pregnancy twelve years ago. A small hernia was present in the scar in the last case. A tumour of the cicatrix was present for a year and a half, two years, and eighteen months respectively. It had given rise to pain at the periods. Tobler's last case concerns a woman aged 30, who had a tumour, 1 cm. in diameter, in the scar of a suppurated appendicectomy wound made six years previously. It contained minute brownish cysts. *Histology:* Dense scar tissue. Islands of endometrial tissue with cysts and tubules. Blood and pigment. No plain muscle present. In the case associated with a hernia the tumour was attached to the apex of its sac. The tubules are continuous at several spots with the peritoneal epithelium.—Lochrane [48] operated upon a II-para aged 38, whose younger child was twelve years of age. Four years previously a laparotomy was performed for "displacement of the womb," and a tumour was noticed three years later in the scar. "It swells and gets very sore and tender at about the time of the periods." Menorrhagia and severe dysmenorrhœa since the last confinement. Operation: A diffuse, fibrous-looking mass, with ill-defined margins, under fascia of right rectus muscle in laparotomy scar. Shut off from abdominal cavity by the peritoneum only. Honeycombed with small cysts with thick dark menstrual-like fluid. The remains of two or three old catgut sutures are present in it. Anterior wall of the uterus, near fundus, attached to site of the tumour by a narrow band consisting apparently only of peritoneum. Right ovary adherent to uterus, enlarged, and contains a hæmorrhagic cyst. *Histology:* Islands of endometrium imbedded in fibrous scar tissue. Epithelium apparently ciliated in places. No mention of plain muscle.—

Lemon and Mahle [47] record nine cases of "post-operative invasion of the abdominal wall." (1) Aged 46. Ventri-suspension. Tumour of laparotomy scar, midway between umbilicus and symphysis pubis, connected with fundus uteri and extending down into right side of abdomen. Noticed for one year. (2) Aged 35. Ventri-fixatio uteri four years previously. Hard irregular mass attached to fundus uteri below laparotomy scar. (3) Aged 38. Suspension of uterus. Mass in scar, adherent to fundus, painful at periods. (4) Aged 43. Ventri-fixation of uterus twelve years previously. Hard irregular mass under scar. Fundus densely adherent to abdominal wall below it. (5) Aged 30. Shortening of uterine ligaments for prolapse five years ago. Mass in lower part of scar, attached to left Fallopian tube $3\frac{1}{2}$ cm. from uterine horn. (6) Aged 27. Salpingectomy four years previously. Operation for adhesions two years later. Mass in scar, adherent to fundus uteri. (7) Aged 36. Ventri-fixation three years ago. Tumour of lower end of scar noticed soon after. Intermittently discharged bloody fluid. Not connected with uterus. (8) Aged 40. Hysterectomy and oöphorectomy six years previously. Mass in scar. (9) Aged 35. Double salpingectomy, right oöphorectomy, and appendicectomy nine years previously. Tumour of scar noticed six years later. Painful and enlarged at periods. Extended to peritoneum with omentum adherent to its inner surface. Not connected with uterus. *Histology:* Adenomyomata. Fibrous tissue. Islands of endometrium. Epithelium occasionally ciliated. Hæmorrhages, blood pigment. Signs of inflammation. Smooth muscle present. First case contains miliary tubercles. Sections through fibrous bridge between tumour and fundus uteri, when it was present, contain no glandular tissue.—Vassmer [88] saw an unmarried woman, aged 24. Ventri-fixation of uterus four years previously. Two catgut sutures were passed through fundus, but its cavity had almost certainly not been entered. Since then periods painful, with a bloody discharge from a small nodule in the scar. Excision followed by recurrence of tumour. Second excision. Fundus attached to scar by a band. *Histology:* Scar tissue. Islands of uterine mucosa, the tubules of which extend to skin and communicate with the surface. Separated from peritoneum by layer of skeletal muscle. The band is built of plain muscle, etc., typical of the round ligament and uterus, and contains no epithelial structures.—Rosenstein [69] saw an immovable firm tumour of a laparotomy scar, at about its middle between umbilicus and pubes, in a woman aged 23, who had undergone an operation for resection of both Fallopian tubes and ventri-fixation of the uterus five years previously. Excision: Peritoneal cavity not opened. *Histology:* Scar tissue containing several "silkworm" threads. Tubules and cysts. Cellular stroma relatively scanty. Blood and pigment. No plain muscle.

I add to these the following case :

An unmarried woman, 36 years of age, had a colotomy and laparotomy performed two years previously for what she believes to be a suppuration in the pelvis. Both openings have since closed. Lately she has noticed a tumour, 2 cm. in its greatest diameter, in the lower end of the laparotomy scar. It is painful and increases in size at the menstrual periods, at which times she also complains of hæmorrhage from the bowel. The tumour was excised. It lay under the rectus sheath; its edges were ill defined. It did not extend as far as the peritoneum. It was firm and consisted of glistening strands of fibrous tissue, in which a few small brownish cysts were scattered. The uterus was not attached to the anterior abdominal wall. *Histology* (Fig. 88) : The tumour consists of very

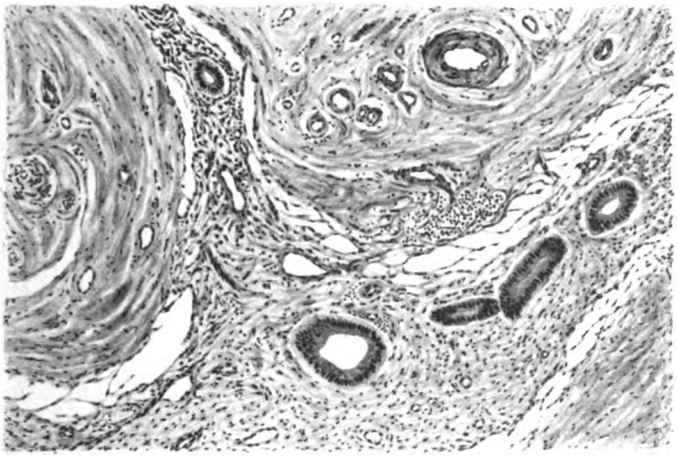

FIG. 88.

Endometrial tumour of laparotomy scar. Magnif., 90.

dense and non-cellular fibrous tissue, which is often wrapped about groups of thick-walled blood vessels, held together by hyaline envelopes of their own. The general fibrous tissue has undergone hyaline degeneration in many places. Plain muscle is entirely absent, but a good many fibres of skeletal muscle are visible, especially near the periphery of the tumour. The islands of endometrium are large and irregular. The tubules are large but few in number. Many are cystic. The stroma is generally relatively non-cellular and fibrillar. It contains many thick-walled arterioles and dilated veins. The looser parts of the fibrous tissue and, to a lesser extent, the endometrial stroma are infiltrated with leucocytes. There are no fresh hæmorrhages and only a few small deposits of hæmosiderin in the stroma. The tubules are empty. The edges of the tumour are ill defined. Its fibrous strands are lost in the surrounding areolar tissue.

These tumours of laparotomy scars can be summarised thus :

They are always found in adult women, between the ages of 22 and 50, with an average age of 36. They are usually associated with disturbances of menstruation, at any rate since the tumour was first noticed. The laparotomy in the scar of which the tumour developed had been performed as long as twenty-five years, or as recently as two years previously. The tumour was noticed after an interval of from a few weeks to twenty-one years. Increase in size of the tumour and pain at the periods are mentioned often, and were accompanied by the discharge of bloody fluid from its surfaces in three cases, described by Lauche,[41] Lemon and Mahle,[47] and Vassmer.[88]

These tumours are restricted to scars of the lower half of the abdomen. Not one has been described above the level of the umbilicus. They can be grouped in accordance with the nature of the original operation.

Group 1 : Ventri-fixation of the uterus. Fifteen cases, namely those of Meyer,[52] Klages,[40] Fraas,[19] Mahle and McCarty [49] (Case 2), Lauche [41] (Cases 1, 2, and 4), Lochrane,[48] Lemon and Mahle [47] (Cases 1, 2, 3, 4, 7), Vassmer,[88] and Rosenstein.[69] In all these, with the exception of Lauche's [41] first case and of Lemon and Mahle's [47] seventh case, the uterus was found to be adherent to the anterior abdominal wall. The peritoneum or omentum is stated to have been involved in the cases of Meyer,[52] Klages,[40] Lauche [41] (Case 2), and of Lemon and Mahle.[47] In those of Lauche [41] (Cases 1 and 4), Lochrane,[48] Vassmer,[88] and Rosenstein [69] it was not implicated.

Group 2 : Operation for perforation or rupture of pregnant uterus. Two cases, those of v. Franque [21] and Cullen.[12]

Group 3 : Hysterectomy. One case, the eighth of Lemon and Mahle.[47] Nevertheless this case is included by these writers in those due to " post-operative invasion of the abdominal wall " by endometrium.

Group 4 : Operations on the Fallopian tubes or ovaries without hysteropexy. Six cases. Sterilisation had been performed in two of Tobler's [87] cases, and an operation for a tubal pregnancy in a third. In Lauche's [41] third case the left adnexa was amputated. Its stump was found to be firmly adherent to the laparotomy scar. Salpingectomy had been performed in two of Lemon and Mahle's [47] cases. In the first of these the cicatricial tumour was adherent to the fundus uteri, and in the other to the omentum.

Group 5 : Operations upon uterine ligaments. One case, the fifth of those of Lemon and Mahle,[47] where the ligaments

had been shortened for prolapse of the uterus. The tumour of the scar was found to be adherent to the left Fallopian tube.

Group 6 : Appendicectomy. Two cases, the third of Mahle and McCarty [49] and the fourth of Tobler.[87]

Group 7 : Uncertain. The case recorded above where laparotomy and colotomy had been performed for " suppuration of the pelvis."

We see that of twenty-eight cases for which data are available, only fifteen had undergone ventral fixation of the uterus. In two of the remainder the operation had to do with the vermiform appendix and not the internal organs of generation.

The naked-eye and histological structure of these tumours of scars is identical with that of those of the groin and umbilicus, and need not be summarised. It corresponds with the uterine mucosa, and there is plenty of evidence of participation in the menstrual function.

We have seen that the peritoneum was implicated by the tumour in several instances. Tobler,[87] indeed, demonstrates histological continuity between the peritoneal epithelium of the hernial sac, to which the tumour was attached, and its tubules.

Unstriped muscle was present in the cases of Klages,[40] Cullen,[12] Mahle and McCarty,[49] Lauche [41] (Cases 1 and 4), and Lemon and Mahle.[47] In Cullen's specimen it formed the bulk of the connective tissue, and in those of Lauche it was present as isolated whorls and knots.

Meyer,[52] Lemon and Mahle [47] (five cases), and Vassmer [88] state that, upon histological examination, no epithelium was found to be present in the band connecting the uterus with the abdominal scar after ventri-fixation. Fraas,[19] on the other hand, found tubules and cysts in the adhesions, but emphasised that they barely extended below the surface of the uterus and were not present in the myometrium. He performed a thorough histological examination of the amputated uterus. In Lauche's [41] second case the tumour was adherent to the surface of the fundus, but the area was not identified with the microscope. Anatomical continuity between the epithelium of the uterine mucous membrane and that of the tumour has therefore not been established in one single case. This fact is sufficient evidence to refute the argument that the uterine cavity was perforated by a stitch at the operation for ventri-fixation and that its mucous membrane had produced a lining for the stitch, which extended into the scar. For it is difficult to explain why this migratory epithelium should not have

survived in the much more congenial atmosphere of the uterine wall if it did so in the scar.

It will be said that this view is obsolete and that it has been superseded by the assumption that the needle used in placing the deep sutures at the operation had perforated the uterine cavity and torn away a fragment of endometrium and implanted it in the laparotomy wound. But what evidence is there of this want of skill and care on the part of the operator? I notice, indeed, that several of the writers who advocate this theory—and it is pretty generally held by British and American gynæcologists—are careful to make it perfectly evident that the original operation was not performed by themselves. It is obvious, of course, that accidents will happen, and that even the best surgeon might wound the endometrium, but I submit that reasonable evidence must be produced that it actually did happen. Unsupported assumptions are not working hypotheses, although the two are pretty often confounded.

Is it probable that a needle, however large it be, provided it have a point, even a very blunt one, would tear fragments of tissue away from their surroundings and push them for considerable distances? This is as improbable as with the smallest needles. The case is entirely altered should the point be broken off, for then a rough surface would result, which would be an admirable agent for laceration and transport. Although I cannot speak from personal experience, I am unable to conceive of even the most careless and inefficient surgeon stitching the uterus to the abdominal wall with a broken needle.

And should a fragment of endometrium be torn away and adhere to the needle or ligature, would it not be arrested almost at once—in the deeper layers of the myometrium—by the resistance and friction offered by this tissue to its progress? Surely the opposite should happen from what we know actually takes place. The most frequent site of these implants should be in the uterine wall, the next under the peritoneum, and the least in the laparotomy scar. We cannot even assume a "predisposition" to account for this anomalous behaviour, since endometrial tumours are infinitely commoner in and on the uterus than in laparotomy scars. And that displacement alone predisposes for tumour formation and the further the tissue be removed from home the more likely it is to flourish is an exploded notion (see, among others, Lauche,[44] not to mention these studies).

The idea that these tumours of scars are the result of transplantation of fragments of endometrium by a stitch is only a modification of the popular "implantation" theory, which is

made to account for all ectopic endometrial tumours and will be discussed towards the end of this paper.* It is born of a desire to explain all related phenomena by the same "cause." But why should not one final effect be the result of divers "causes," using this word in its scientific sense to mean "sequences of events"? There are no reasons, philosophical or scientific, why it should not. Even though it be definitely established that endometrial tumours of the ovaries, let us say, are the result of implantation of fragments of uterine mucous membrane, it does not necessarily follow that all the instances found in other regions must be due to the same "cause."

D. Ectopic Intra-abdominal Endometrial Tumours

There remain the endometrial tumours of the abdominal cavity outside the uterus and Fallopian tubes. It is these that have received much attention of late from gynæcologists. Large numbers have been recorded. From our present point of view they have two principal features of interest. They are diffuse and often multiple, and in a good many cases even more or less generalised in the lower half of the abdomen, and they are superficial. I mean by this that they are connected with the peritoneum, being merely shut off from it by adhesions which are obviously secondary. Certain tumours of the ovaries appear to be excepted from this statement, but even they are surrounded by adhesions, which are often occupied by the tissues of the tumour, and it is far from certain that these "tarry" cysts, even when they occupy the centre of the organ, do not always originate upon its surface.

Although the intra-abdominal tumours are often multiple, a good many cases are on record in which only one circumscribed area was affected. This is true of every viscus on which they are found. I propose to select from these isolated cases some of those of the gut, since they are least well known and present several features of pathological interest. I begin by describing a case for which I have to thank Mr. E. C. Hughes, who operated upon it in private a few years ago.

The patient, a married woman 40 years of age, suffered

* Geller [23] found superficial groups of uterine glands surrounded by stroma in the scar of a uterus which was amputated after two Cæsarian sections. Its anterior surface was covered with adhesions. These structures were not connected with either the serosa or the mucosa. Geller concludes that they are the result of "stitch implantations," but, since they were placed a short distance below the peritoneum in a scar, the argument that they are derivatives of its epithelium is equally plausible, to say the least of it.

from symptoms of intestinal obstruction. There is no history of menstrual disturbances. The affected piece of intestine was not adherent to the neighbouring structures and no anomalies of the genital organs were found at the operation. The specimen, when I saw it, consisted of 8 cm. of large intestine, corresponding with the rectum, at about the middle of which there was a semicircular projection of its wall, 2 cm. in diameter. It was covered by the mucous membrane and nearly occluded the lumen. The projection corresponded with a narrow deep constriction of the outer surface, over which the peritoneum was rough and thickened. Upon making an incision through the specimen at right angles to the constriction it was seen that the tumour consisted of an invagination of the whole thickness of the anterior wall of the gut. Its base was formed of dense scar tissue, the strands of which radiated outwards like the ribs of a fan and had pulled upon, considerably thickened, and

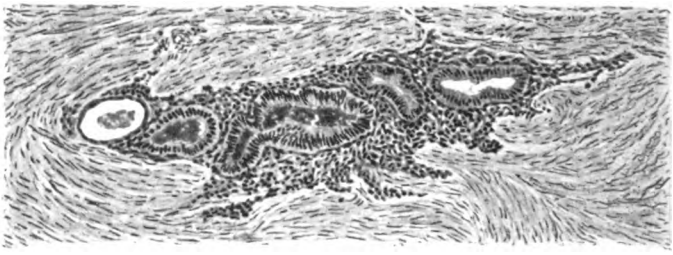

FIG. 89.

Endometrial tumour of rectum. Island surrounded by hypertrophied intestinal muscle. Magnif., 90.

almost completely obliterated the natural layers of the intestinal wall. The mucous membrane was smooth and freely movable over the tumour, and presented no signs of ulceration. The patient has remained free from symptoms since the operation five years ago.

Histology (Figs. 89 and 90): The characteristic tubules and cysts, surrounded with cellular stroma, are present in the shape of irregular islands which are relatively large in the subperitoneal tissue, smaller and less numerous in the muscular coat, and again more numerous and well developed in the sub-mucosa. The stroma has the cellular structure of endometrial tumours in general and the mucous membrane of the uterus. It contains dilated lymph spaces, which are represented in Fig. 90. The islands inter-communicate by means of processes, as can be demonstrated in serial sections. The tubules are tortuous and occasionally branched. They are lined with a single layer of epithelium. This is columnar as a rule (Fig. 89), but varies in height with the degree of dilatation of the tubules and cysts in the usual manner. Fig. 90 shows a large sub-mucous cyst, the roof of which, where it abuts

directly upon the *muscularis mucosæ*, is lined with flat cells, whereas the epithelium of the rest of its circumference, which is surrounded with cellular stroma, is cubical. The cysts are most numerous and largest in the sub-mucosa, where the *muscularis mucosæ* appears to offer a barrier for their extension inwards. It follows from this that no islands are found in the mucous membrane, which is perfectly healthy, except for a slight catarrhal reaction of the crypts of Lieberkuehn. The obvious fact that there is no anatomical continuity between the intestinal epithelium and that of the tumour would therefore not be mentioned were it not of great importance. Within the muscular coat of the intestinal wall the islands are narrow and elongated and obviously adapted in shape to the septa

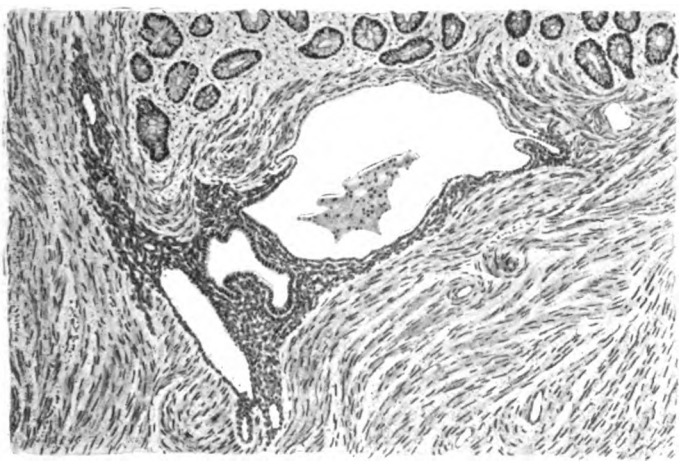

FIG. 90.

Endometrial tumour of rectum. Island of endometrium in *sub-mucosa* separated from mucous membrane by *muscularis mucosæ*. Magnif., 50.

between the muscular bundles. The muscle itself is hypertrophied and sclerosed. Nowhere do its fibres form independent sheaths or *tunicæ propriæ* for the islands. In the sub-serous coat the islands are large and placed in the midst of the areolar tissue and sub-peritoneal fat. It is unfortunate that this part of the specimen was damaged at the operation, since the peritoneal epithelium is nowhere preserved and its relations with the tubules of the tumour are therefore lost. There is abundance of evidence of menstrual activity in the shape of fresh clotted blood (Fig. 89) and pigment cells in the tubules and cysts, and of hæmorrhages and iron containing pigment in the stroma.

Similar cases, in which a segment of the gut alone was affected, without apparent implication of other abdominal

viscera, are few in number. The tumour was situated in the sigmoid in the cases of Meyer,[55] Hueter,[32] Lauche,[41] Tobler,[86] de Jong,[37] and Gross.[27] The vermiform appendix was affected in Hueter's [32] and Suzuki's [84] cases, and a loop of ileum, about 8 cm. above the ileo-cœcal valve, in de Jong's [35] first case. Except in Suzuki's [84] tumour of the appendix, which is a definite circumscribed adeno-myoma, the lesion was more or less ill defined and presented itself as a thickening and roughening of the peritoneum, with scarring and hypertrophy of the intestinal wall and invagination of parts of it into the lumen. De Jong's [35] specimen of the ileum is of particular interest, since the affected loop contained two large areas of stenosis, as well as eight small scars and nodules upon its peritoneal surface. Most writers mention that the mucous membrane of the intestine was not implicated, being movable and free from ulceration. The youngest sufferer was aged 34 and the oldest, with the exception of Gross' [27] patient, who was 62 years of age, was 48. I need hardly state that they were all women. Several suffered from dysmenorrhœa. Uterine fibroids coexisted in the cases of Lauche [41] and Suzuki.[84] Hueter,[32] Tobler,[86] and de Jong [37] found ovarian cysts. The latter [36] also records the presence of a cyst of the ovary with "tarry" contents, which was removed some time after the first operation. In one of Tobler's [86] cases the tumour of the sigmoid flexure was attached to the left Fallopian tube.

The last two cases lead us to others in which the endometrial tumour of the gut dominated the clinical picture, although it was associated with similar tumours elsewhere. I mention only some of the earliest cases recorded. Cullen [12] describes an "adeno-myoma" of the sigmoid near the pelvic brim with an independent tumour of the recto-vaginal septum. —Mahle and McCarty [49] mention a tumour of the sigmoid, which was adherent to a mass around the uterus and bladder and associated with "tarry" cysts of both ovaries.—Sampson [73] describes twelve cases of endometrial tumours of the ovaries with similar lesions of various parts of the lower intestinal tract.—Dougal [13] records an "adeno-myoma" of the vermiform appendix associated with, but independent of, a similar tumour of the sigmoid and a "tarry" cyst of the left ovary. The appendix was long and firmly adherent to the lateral wall of the pelvis. It was kinked, and its apex formed a globular tumour. The mucous membrane was unaltered.

There is but a step from these cases to others with generalised "adeno-myosis" of the greater part of the pelvis. The case of Semmelink and de Jong [80] is a type of these. Hæmor-

rhagic cysts of the left ovary were associated with very extensive "adeno-myomatous" lesions of the internal organs of generation, affecting all parts except the Fallopian tubes and cervix, and with large endometrial tumours of the uterus and intra-pelvic part of the right round ligament.

A glance at the recent literature (*e.g.* Bailey [4]) shows that one of the organs most commonly affected with endometrial tumours is the ovary, whether the lesions be more or less generalised or not. This led to the establishing of the so-called "Sampson complex," of which a good deal will have to be said presently. For the moment we need but point out that areas of endometrial tissue are of frequent occurrence on the surface of these organs, as well as within their substance, where they present themselves as isolated or multiple so-called "tarry" cysts, their contents being thick brownish bloody fluid comparable with the retained inspissated menstrual blood to be found in cases of atresia of the hymen, etc. The ovaries are always surrounded by dense adhesions, which bind them firmly to the neighbouring tissues.

The first specimen was described by Russell [71] in 1899 as "aberrant portions of the Muellerian duct found in the ovary." The greater part of the organ, with the exception of the hilum, was occupied by blood-stained cysts. There was a shallow groove upon its posterior surface covered with endometrial granulations.—Pick [67] described four cases a few years later as "*adenoma endometrioides.*" The cysts contained "thickish, syrupy, chocolate brown, or reddish contents, which resemble entirely the retained blood of atresias of the female generative organs and are no doubt caused by participation of the endometrium-like tissue in menstruation."—It was not until 1921 that general interest was aroused in these lesions of the ovaries by Sampson's [72] writings.—Blair Bell [6] and Shaw and Addis [81] were the first to describe cases in this country in the following year.

The intra-abdominal endometrial tumours present themselves as roughenings of and granulations upon the peritoneal surface of the organs affected. They are covered with dense adhesions, between which they extend. Fibrosis takes place and the organ is infiltrated with scar tissue, in which reddish areas of endometrium and cysts filled with tarry fluid are usually present and extend downwards for a considerable distance. Hypertrophy of the involuntary muscle of the part takes place. This may be localised, with the formation of circumscribed tumours identical in appearance with fibroids, or more or less diffuse. The cysts are usually small, but often attain a moderate

size in the ovaries. The largest seen by Sampson [74] measured 15 cm. in diameter.

Very little need be added to my description of the histology

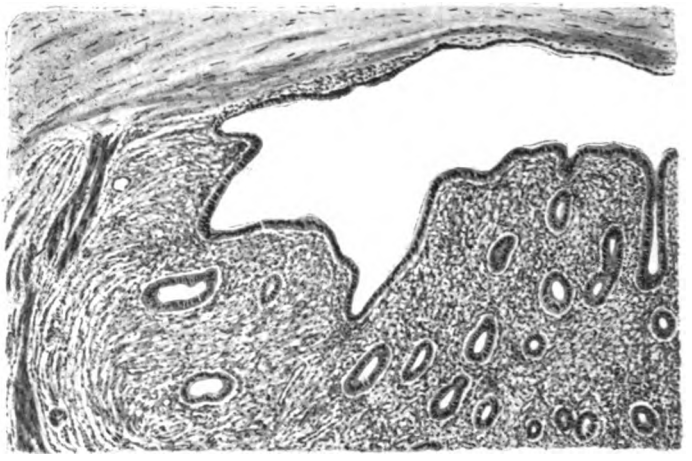

FIG. 91.
Endometrial tumour of ovary. Resting stage. Magnif., 35.

of the tumour of the rectum. Cilia have been described in a few instances. The islands of endometrium attain their greatest size and most perfect approximation to the structure of the

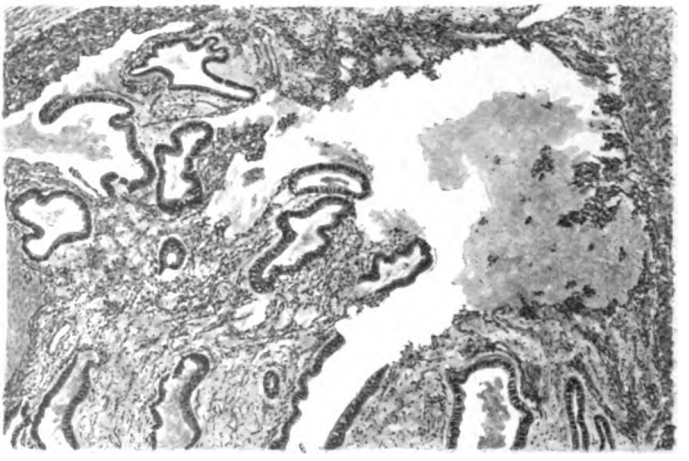

FIG. 92.
Endometrial tumour of ovary. Menstruation. Magnif., 50.

mucous membrane of the uterus in the cysts of the ovaries. Very perfect miniature uteri are produced. Fig. 91 illustrates part of one in the resting stage, and Fig. 92 at the height of menstruation.

A great part of the increase in size of the affected organ, and especially should this be the intestine, is due to hypertrophy and fibrosis of its muscular coat. These changes are associated with more or less pronounced proliferation of the connective tissue cells and signs of a mild degree of inflammatory reaction. The greater part of the muscle found in these tumours represents the hypertrophied pre-formed musculature. It follows from this that its bundles are not generally arranged around the islands of endometrium after the manner of a *tunica propria*. In fact it is easy to see that it is the islands that are adapted and have followed the outlines of the preformed bundles of muscle by spreading between them and pushing them aside. Hence we find in tumours of the intestine that the islands are elongated and few in number within the muscular coat, and that they are much larger in the *sub-serosa*, the *sub-mucosa*, and the narrow space between the longitudinal and circular muscular layers. Again, the fact has been emphasised by all the writers upon endometrial tumours of the gut that the *muscularis mucosæ* offers very considerable resistance to the invasion of the mucous membrane by the tissues of the tumour.* Thus we see in Fig. 90 that the epithelium of the sub-mucous cyst in its endeavour—if I may use this expression—to enter the mucosa has flattened itself against the *muscularis mucosæ* without being able to penetrate it. This is so in all parts of the specimen and the general rule in these tumours of the gut. In Meyer's [55] tumour of the colon, however, a polypoid fold of mucous membrane projected into the intestinal lumen. It was ulcerated and partly denuded of epithelium. Meyer traced uninterrupted newly-formed tubules from the epithelium of this polypus through all the layers of the intestinal wall into the mesentery, where they were in close apposition with and often invaginated the lymphatics, but they never penetrated their endothelium or invaded their lumen. Where they passed through the *muscularis mucosæ* its fibres were separated by them. Lauche [41] tells us that the only spot at which his tumour had entered the mucosa was at the site of a lymph node, where the *muscularis mucosæ* is often physiologically defective. In Tobler's [86] tumour an endometrial tubule was present within a lymph node in the mucous membrane. In de Jong's [37] case the tissues of the tumour had penetrated the mucosa at one spot only, but no mention is made of the presence of lymphoid tissue here.

The histology of Gross' [27] tumour of the sigmoid differs

* This fact, as well as the absence of continuity between the epithelium of the intestine and the tumour, removes the necessity for discussing the possible origin of endometrial tumours of the gut in intestinal epithelium.

from that of the majority of endometrial tumours, agreeing with those described by Artusi [2] and by me [61] in the round ligament. His patient was 62 years of age. The climacteric had occurred sixteen years earlier. The tubules were markedly degenerated and cystic. Their epithelium was flat and atrophic. The cellular "endometrial" stroma was replaced by much denser connective tissue. There was complete absence of signs of hæmorrhage into the tumour.

It is a well-known fact, fully established by Meyer and others, that direct anatomical continuity can often be shown to exist in endometrial tumours of the peritoneal surface of the uterus and Fallopian tubes between the tubules of the tumour and the epithelium of the peritoneum. This continuity has been established in tumours of the gut upon several occasions. It is true that Meyer [55] was misled in his original communication and believed the epithelium to be intestinal in origin. Recently, however, he [58] has come to regard it as a derivative of the peritoneum. Hueter [32] has established the fact that the epithelium of his tumour of the vermiform appendix is derived from the peritoneum. This was inflamed, roughened, and thickened, and covered with a thick layer of granulations with cracks and spaces lined with peritoneal epithelium. He demonstrates that tubules are given off from the corners of these spaces and the sides of the mesenteric reflexion on to the appendix. He regards the inflammation of the peritoneum as the effective cause of the tumour. He was unable to furnish this proof in his second case. Lauche [41] shows that the epithelium of his tumour communicates at one spot with the peritoneum. Here several tubules open into the peritoneal cavity, and its lining is replaced for a short distance by tall columnar epithelium. De Jong [37] successfully demonstrates the same state of affairs in his second case. The glandular proliferation is much more extensive on the serosal surface of the intestine than elsewhere. He traces the development of tubules on the peritoneum and concludes that it is impossible to assume anything but a peritoneal origin for them. Suzuki [84] describes communications between the tubules of his tumour and the *serosa* where this is reflected on to the remains of the vermiform appendix.

The endometrial tumours raise many questions of pathological interest. We will begin by considering their mode of growth. We have seen that the tumour may be isolated and well defined for the naked eye, but that it is often diffuse and even generalised over a comparatively wide area. But the

microscope usually shows that the edges are not as sharply defined as the gross appearance of the specimen indicates. The islands of endometrium which we believe, as stated above,* to be the only essential constituents of the tumour, are intimately mixed with bundles of fibrous tissue and involuntary muscle. The former are always—and the latter can generally be shown to be—derived from the tissues of the part affected.

There are three ways in which these tumours grow: by apposition, as in my first tumour of the groin, where fresh islands of endometrium were added to it by a process of fibrosis around them, to be absorbed into its substance; by expansion, as in innocent tumours in general; and by a form of growth which bears a somewhat close resemblance to the infiltration of malignant neoplasms.

This last form can be studied best in the tumours of the intestines. Here, as elsewhere, we see islands which consist generally of tubules surrounded by cellular stroma, but in which either constituent may be absent. They permeate the areolar tissue of the sub-peritoneal and sub-mucous layers, in which they expand and attain a considerable size. In the dense muscular coat they are narrow and elongated and, as has been said above, adapted to the shapes and contours of the muscle bundles. They show a tendency to surround the lymphatics (Meyer's [55] tumour of the gut), but not to invade them. They push the peritoneal epithelium aside and form nodules under it, and surround blood vessels and nerves. But there are no signs of destruction of tissue. When the islands reach the *muscularis mucosæ*, a compact layer of closely interwoven fibres with few gaps, they do not penetrate it except where it is naturally defective, as under lymph follicles (Lauche [41]) and at the points of entry into the mucosa of the blood vessels and lymphatics. In all these respects their mode of growth differs from that of malignant neoplasms.

There is no destruction of tissue, only fibrosis and atrophy, associated with plastic inflammation. These are reactions of the tissues to the irritation or foreign body action of a mass of cells which ought not to be there. They are analogous to the fibrosis seen around every foreign body, be this introduced from outside the organism or the result of the action of a pathological change upon its own tissues. They are comparable with the capsule formation of innocent tumours. They differ from it in that they are diffuse, since the "foreign body"—in this case the islands of endometrium—is extremely irregular

* All the arguments brought forward in the case of the tumours of the inguinal region apply to endometrial tumours in general.

and branched and every one of its semi-independent parts induces its own reaction. This reaction is insufficient to inhibit the growth of the foreign body, which increases in size and complexity of shape, and is thus surrounded by ever-increasing fibrosis.

Again, the inter-relations of the epithelium and stroma are of interest. Both tissues grow independently of each other, since they may be present alone. But we have seen that it is one of the most constant characteristics of these tumours that the degree of dilatation of the tubules and the height of their epithelium varies inversely with the amount of stroma present around them. This is not invariably so, since "naked" tubules furnished with tall columnar epithelium are occasionally met with, but it is the general rule. In the absence of the supporting stroma the epithelium generally atrophies. Its vitality is impaired. Growth proceeds most readily when both tissues are associated. In this respect endometrial tumours differ from malignant neoplasms.

Yet again, it is a suggestive fact that these tumours are not found above the level of the umbilicus, whether they be extra-abdominal or connected with the peritoneal surface of the gut. I would point out that this is opposed to our ideas of malignancy. For why should not the cells of a tumour which spreads by "dissemination" be carried to and settle on the whole of the peritoneum if they can flourish in the lower half of the abdominal cavity? There must be a factor in action which is not at work in malignant tumours.

But there is yet another factor, inoperative in malignant blastomata, without which the growth of these tumours is inhibited. I refer to an age factor, associated in one way or another with the period of reproduction. Not only are these tumours unknown in children, but we have seen that they undergo atrophy and that their physiological action ceases after the menopause. This was so in the specimens described by Gross [27] Artusi,[2] and the present writer,[61] the ages of the patients being 62, 68, 66, and 55 respectively.

This raises the question: Why are endometrial tumours never found in males? I presume for the same reason that the uterine mucosa is not present in this sex. This answer is more sensible than it appears to be at first sight.

It would appear that the growth of these tumours is peculiar to them and not shared by others. But pathological happenings are nothing new, but merely exaggerated and distorted forms of physiological processes. We must therefore look for a prototype in the healthy body. I believe that we find it

in the epithelium of the uterus, the tubules of which normally are not bounded by definite muscular tunics, but extend for short distances between the fibres of the myometrium. How exaggerated this growth may become is shown by the great proliferation and extension of the uterine epithelium which is generally accepted to be responsible for the production of the internal endometrial tumours or "adeno-myomata" of the uterus. The uterine epithelium has the "habit" of extending into the areolar septa between the fibres of its muscle. These offer no great resistance to it when they are loosened and separated by exudate. But when the epithelium reaches a dense layer of fibres, like the *muscularis mucosæ* of the intestine, its progress is stopped except where there are gaps in this tissue. Epithelium always tends to cover raw surfaces with which it comes in contact, a fact which is well illustrated in Fig. 37 (IV). It extends between granulations and into tissue spaces, provided these be loosened by inflammation. And a mild degree of plastic inflammation is present in these tumours at their stage of active growth at all events. I can see no fundamental differences between their mode of growth and that of the majority of epithelia in pathological states (see Lauche [44] upon heterotopias of the intestines). It is exaggerated, but not to the extent seen in the infiltration of malignant neoplasms.

Halban [29] propounds a theory which I mention here to dismiss it. He assumes that parts are separated from uterine tubules and pass between the cells of the muscle to enter the lymph spaces. In these they traverse the uterine muscle as far as the serosa (giving rise *en route* to internal endometrial tumours). The wandering uterine glands may leave their physiological home by way of the lymphatics and stream outwards in all directions. The correctness of this view is said to be proved by the presence of characteristic uterine tubules in the regional lymph glands. Halban, however, does not describe them more closely nor figure them. I have not seen these inclusions in lymph glands, but the study of a good many sections of intra- and extra-uterine endometrial tumours has convinced me that their cells most carefully avoid the interior of lymphatics. They surround them closely enough but do not enter them.

I have taken it more or less for granted hitherto that these tumours are truly *endometrial* and not merely *endometrioid* in nature, using these terms in the histological and not the histiogenetic sense. I have maintained, and still do so, that the sole criteria we possess in forming our opinion of the nature

of a tissue, be it normal or part of a neoplasm, are its structure and evidences of the performance of physiological functions by its cells. If the tumour is identical in these respects with the uterine mucous membrane the two are identical in nature. And this they are regardless of their histiogenesis. I have brought forward sufficient evidence, collected chiefly from the literature, to convince myself and—I hope and, indeed, assume —others of the correctness of the statement that these tumours consist of genuine endometrium.

These considerations lead us to one of the principal reasons why this paper is written. We must ask: What is the status of endometrial tumours? Are they neoplasms or blastomata in the generally accepted sense of the term or are they hyperplasias?

Everyone who has dabbled in zoological classification even in the superficial way that I have must have been struck by the difficulties that arise when he attempts to define a species. Whereas the majority of species are separate stable entities, many remain which it is impossible to define. They are unstable, in a state of flux, and connected with allied species by innumerable intermediate characters. The only logical conclusion that can be drawn, in my opinion at least, is that species are accidents, that they are transient forms which owe their preservation to circumstances acting on them from without. They are the creatures of their environment. Should they harmonise with it they survive unchanged for countless ages. But should the environment change they cease to be, since they are compelled to adapt themselves to the altered surroundings by modifications of structure and are thereby changed into new species, or wiped out of existence if they cannot adapt themselves.

Similar difficulties arise when we try to establish a genus. Whereas it will contain many good species, which fit well into the confines of its definition, a turbulent minority will remain that do so only in part, and appear to belong to other closely related or even widely distant genera in one or more of their characters.

When we try to classify tumours we are confronted with the same difficulties. Whereas many tumours conform in every respect with our definition, others remain that refuse to do so. The size of this minority is only realised after considerable experience and knowledge have been acquired.

I have said above that species are the creatures of their environment. What applies to the organism as a whole applies to its parts. Every cell is the creature of its environment.

This statement requires definition. I do not for one moment deny that certain races and individuals are endowed with attributes that are absent or much less highly developed in others. I regard the popular cry, "All men are equals," as unmitigated folly. But what is a strain, or breed, or race more than the cumulative effect of an ancestral environment, the action of which is strong enough to be transmitted to the offspring? Although I deny that certain diseases, or malformations, or indeed the most constant and physiological characters are inherited *sensu stricto*, I cannot get away from the fact that the potentiality for them is inherited. But the potencies which are present in the zygote—no matter whether they reside in the chromosomes or elsewhere—will not be realised unless they be subjected to the action of a suitable environment during development. There would have been no progress, no evolution, without variability, and this factor itself justifies its name in the very width and breadth of its limits. But *variability* by itself achieves nothing, since it requires to be acted upon during development to find its expression as *variation* in the finished organism.

Variability admitted, nowhere in biology can it be more clearly realised than in pathology that the cell is the creature of its environment. I define pathology as the science which deals with the *normal* or *physiological* reaction of the cells to an *abnormal* or *pathological* environment. It follows from this that there is nothing new or un-physiological in the changes undergone by the cells, since they are the expressions of natural potencies, with which they are endowed from the beginning, but which are not evoked or developed in a normal environment. All pathological changes are merely modifications of physiological form.

And this applies to tumours as well as other pathological states. Our difficulties in classification are the result of our ignorance of the change—or sequence of changes—of the environment which has compelled the cells to assume blastomatous growth. This applies in the same way to zoological classification. We are unable to catch a change of the environment. The most we can do is to catch its expression in the resultant change of structure. The zoologist bridges the gap with the geological record which, fragmentary though it be, has led to brilliant results. The pathologist has as yet scarcely begun to do so by trying to establish sequences of changes of form which lead to, if they do not end in, tumour formation.

We have seen that the tumours we are considering in this paper are pieces of endometrium, with the same structure and

the same functions as the uterine mucous membrane. They menstruate when it does * and even occasionally produce a decidua.

Must we classify accessory organs of this remarkably high degree of organisation as true neoplasms or blastomata? If not, how are they related to them, if at all? It is exceedingly difficult to answer these questions.

The majority of British and American writers dismiss the whole difficulty summarily by adding the suffix " oma " to their description of the specimen. They thereby include it with the blastomata. German writers, however, realise that the difficulty exists. Hueter,[32] de Jong,[36, 37] Lauche,[41] Tobler,[86] Meyer [58] and others discuss it, but generally conclude that the evidence is in favour of a hyperplasia of one kind or another. Their opinion is influenced by ætiological considerations. Lauche,[41] indeed, separates endometrial tumours of the umbilicus † from the others, since he regards them as derivatives of remnants of the exocœlom of the embryo. These consist of *undifferentiated* cœlomic epithelium and mesenchyme, that are stimulated to grow and undergo differentiation into glandular epithelium and cellular stroma or involuntary muscle respectively by changes that produce a fibro-adenomatous proliferation of the fully differentiated peritoneum of the abdominal cavity. Umbilical tumours are therefore true blastomata.

But apart from the fact that there is not a particle of evidence that embryonic cell-rests persist indefinitely in the *undifferentiated* state (see Studies II and III), our ideas of pathology in general and tumour formation in particular are not advanced or clarified when we simply assume that a stimulus—or change of the environment, as I prefer to name it—when it affects undifferentiated cells gives rise to a tumour, whereas it does not if the cells are differentiated. It really means that it is impossible to establish sequences of events in tumour formation, since no sequence ends in it unless the unknown—and unknowable—factor of " persistence in the undifferentiated state " be present. It reduces tumour formation to the mystery of the days of Cohnheim.

The position of these writers is this: If inflammation, regeneration, or metabolic changes of a general kind can be

* This function depends upon peculiarities of structure and can only be compared with the " vicarious menstruation " of other mucous membranes in that the hæmorrhages are caused by rupture of vessels at periods of high blood pressure in both cases. The analogy ceases here, since in the one it forms part of a periodic physiological cycle of rejuvenescence and in the other leads at most to haphazard necrosis and desquamation of cells.

† Together with certain instances in the inguinal region.

shown to be the chief and apparently sole factor in the production of an anomaly, this cannot be a true blastoma. I agree with de Jong,[37] who says that there is but little sense in separating inflammations and tumours sharply from each other. It is my belief that they cannot be thus separated, and that many blastomata are the expressions of reactions of the cells to inflammation, regeneration, and metabolic upsets. Since, however, many of the steps of the sequences which end in tumour formation are unknown, we are unable as yet to say why they do so in one case and not in another.

I pointed out in Study IV, when discussing the acquired hyperplasias, that they are of frequent occurrence in cirrhotic livers as multiple bile-stained nodules which fail to unite with the bile ducts. They thus resemble—and actually are—tumours. But they are also obvious attempts at compensating the antecedent destruction of liver cells. Since cause and effect are obvious, they are therefore classed among the compensatory hyperplasias except in the rare cases when they are found in apparently healthy livers. Their ætiology is obscure in these cases. They are assumed to originat in congenital anomalies and relegated to the tumours.

The position I would occupy is this: In judging the status of an anomaly and determining whether it be a tumour or not, we should remain uninfluenced by questions of ætiology and classify the finished article as we see it on its own merits. It is a strange fact that Albrecht [1] was almost the only pathologist to adopt this attitude. He established the hamartomata, which are both tumours and malformations. I would extend his hamartomata to include practically all tumours, since I am constantly impressed by their similarity with other pathological anomalies. These are far more striking than the ways in which they differ from them.

The chief way in which all * tumours differ from the normal tissues is by being less perfectly organised. The imperfections are structural and functional. They vary, however, within wide limits, but are sufficiently well marked to justify the statement that tumours subserve no useful functions. This is true even of endometrial tumours,† which are the most highly organised and functionally active of them all. But if we include them in the genus *Tumor* for this reason we must also include various other conditions: nodular compensatory hyperplasias, many accessory organs, and even parasitic twins. Our difficulties appear to me to be insuperable.

* We must omit malignancy, since it is not universally exhibited.

† I cannot enter here into the question if they are responsible for certain cases of ectopic gestation, as has been repeatedly maintained.

The conclusion I reach, if indeed it be one, is that endometrial tumours are neoplasms in some respects, whereas in others they are much more closely related to a physiological tissue than the majority of malformations.

This may appear a lame ending to many, since it is decidedly not a solution of our difficulties. But I see great merit in this. It teaches us the futility of trying sharply to define one pathological state from another. Since, as I believe, tumour formation is one of the potencies of every not too highly differentiated cell and depends upon changes of its environment, we must expect to find many intermediate forms which defy classification. Every attempt to give the word " tumour " a definition has failed, and the most we can say of " blastoma " is that it is a tumour which happens to fit our definition. The reasons for this are obvious. Species do not exist in nature except as more or less transient adaptations to their environment, as expressions of an almost unbounded variability. The latter is seized upon and moulded by the former. Many potencies find expression and are crystallised to reappear in future generations, and others are suppressed and maybe lost. New forms are produced which are stable enough as long as they harmonise with their environment, but they disappear when they no longer do so. Evolution is constantly at work not only in individuals, but in all the cells of their bodies. It is the privilege and the as yet unattempted duty of pathology to show to general biology and physiology how great the changes are that the environment produces and how readily they are produced.

We must now turn to the consideration of the histiogenesis of these tumours and attempt to answer the question: In which tissues do they originate? We have seen that they are built of uterine epithelium and endometrial stroma, with which involuntary muscle is frequently associated.

One of three structures is usually assumed to be the tissue of origin of endometrial tumours: a cell-rest or error of development, an implantation of a fragment of uterine mucous membrane, or the peritoneal epithelium. We will discuss these separately.

(1) Dysontogenetic theories. The chief and best attested of these concerns the Wolffian body. We have discussed it above and tried to show its inadequacy, and need not do so again.

Many writers claim that these tumours originate in displaced pieces of Mueller's ducts, which were carried to the spot required by them during development. Here, as in the

case of the Wolffian body, three requirements should be satisfied before a theory of this kind need be considered. A path must be found by which they reach the spot. They must be shown to have reached it in the embryo. They should be shown to persist here after they have reached it. The attitude of so many writers who naïvely assume, with Pick,[66] that cells which are displaced from their natural surroundings possess the property of resisting physiological atrophy and sooner or later undergo independent proliferation, is contrary to the evidence, as I have tried to show many times. Again, it is a physical impossibility for pieces of Mueller's ducts to be displaced into the umbilicus, for instance, except possibly in certain monsters, not one of which would survive.

Accessory Muellerian ducts are not found except in the immediate neighbourhood of the ducts themselves. They cannot, therefore, be invoked to explain our tumours except when they occur in the pelvis close to the uterus and Fallopian tubes. Even the ovaries must be excluded according to Meyer [56] for two reasons. Firstly, it is improbable that the epithelium on the surface of the ovary and that of Mueller's duct are so nearly related that the former should produce Muellerian epithelium more readily than that the latter should give rise to follicular epithelium. Secondly, the anatomical relations between the ovary and the Muellerian fold are not so intimate at first that we are justified in assuming a displacement of cells from the one to the other.

The second argument appears to me to be incontrovertible. The first, however, requires amplification. Meyer modifies it himself with the statement that he has no wish to deny to the surface epithelium of the ovary the potency to produce cylindrical and ciliated cells. It will be free to do this as soon as it is not forced to form follicular epithelium by its relations with the normal ovarian tissues. But this does not prove a closer relationship with the epithelium of Mueller's duct than with that of the remainder of the peritoneum.

Meyer takes an epigenetic view of development, as every pathologist is bound to do. He realises that cells undergo differentiation in the normal direction because they are compelled to do so by the orderly action of influences reaching them from without—by a normal environment—and not because it has been decreed by Fate that they must assume this form and no other. We may therefore ask: Why are the ducts of Mueller only produced in a localised area of the embryo and, so far as we know, never outside its limits? We can only answer this question in the most general and vague way. There

must be influences exerted directly or, more probably, indirectly by another organ or group of cells which compel them to do so. And since the mucous membrane of the uterus is present only in the female sex, and the ovaries make their appearance in the embryo before the protophase of this organ is developed in a fold of peritoneum, it is only reasonable to assume that it is the ovaries that exert them.

We can visualise, though dimly, why Mueller's ducts occupy only one area and why they are not scattered over the greater part of the cœlomic cavity for the comfort of pathologists in general and Cohnheim's school in particular. I can see that differentiation in a certain direction must be but the last step of an orderly series of reactions in response to a long sequence of changes of the environment. We ought not to assume that all the cells of the peritoneum are identical at the moment of the appearance of Mueller's ducts even if they be originally. Their spatial relations, not to mention others, differ among themselves. They must have been subjected to differences of environment during the whole of their life histories. The nature of all these together must have been of a kind to compel this particular differentiation to take place only at one definite spot. The cells here are not "predisposed" for Muellerian epithelium, they are "prepared" for it.

We see that it is impossible for fragments of Mueller's ducts to be displaced into distant parts of the body and that the evidence is opposed to the view that they are differentiated outside a strictly limited area of pelvic epithelium in the embryo. We can thus dispose of theories that assume that ectopic endometrial tumours arise in accessory Muellerian ducts, except possibly in the broad ligaments.

We can dismiss theories that postulate a developmental anomaly or predisposition of a general and undefined sort. It is, of course, as impossible to disprove them as it is for their authors to prove them. It must be confessed that they generally do not even try to do so.

(2) Implantation theory. This is associated with the name of Sampson,[72, 73] who propounded it. He makes the following assumptions: Retrograde menstruation, by means of which menstrual blood and fragments of uterine mucosa enter the abdominal cavity, is a relatively frequent phenomenon. The blood irritates the peritoneum where it comes in contact with it and thus enables the fragments of endometrium to settle upon its sticky inflamed surface. This most frequently happens on the ovaries. The fragments are quickly acclimatised and grow and flourish exceedingly and produce the tarry cysts of

the ovaries. The ovary acts as a "sort of intermediary host, hotbed, or incubator," which not only causes the displaced uterine cells to proliferate with increased vigour but to differentiate freely into functioning endometrium. The menstrual blood which results from these activities accumulates, sooner or later ruptures the cyst, and scatters fragments of its endometrial lining on to the peritoneum. These, having been duly incubated, settle readily upon the peritoneal surface of the organs with which they come in contact, and proliferate to give rise to endometrial tumours.

This theory stands or falls upon the soundness of its assumptions. We will discuss these separately.

I must leave it for gynæcologists to decide if retrograde menstruation be an event of frequent occurrence. Several of those I have consulted think that there is little evidence in favour of it except that postulated by Sampson's theory to account for these intra-abdominal endometrial tumours. Again, these do not appear to be more frequent in cases of obstruction or atresia of the lower segments of the organs of generation than in others. Upon general principles and with due regard for the direction of the currents set up by ciliary action in the Fallopian tubes, I incline to the opinion that retrograde menstruation is not an established phenomenon.

Is menstrual blood more irritating than blood from other sources? In any case, it can only enter the abdominal cavity in small quantities at a time, and we know that the peritoneum is well able to deal with small amounts of extravasated blood. And unless menstrual blood has an intensely irritating effect, almost comparable with that of a blister or cautery, why should it settle with great regularity upon the surface of the ovaries and not be carried by gravity into Douglas' pouch? And should it have this necrosing effect, why are not the fragments of endometrium carried by it killed almost instantly? Sampson should have told us that—and why?—the uterine mucosa is more resistant to its action than the peritoneum.

Far more important is the state of the fragments of endometrium that are desquamated at the menstrual periods. They consist of surface and tubular epithelium to which a small amount of stroma adheres. This stroma is infiltrated with œdema fluid and generally with blood. It must be remembered that these fragments are cast off from the superficial layers of the endometrium as the result of a physiological process which ends in their death. Evidence of necrosis and nuclear degeneration is usually present, but these changes are much more apparent in some of the cells than in others. One would

expect, from *a priori* considerations, that these fragments are most unsuited to assume a mode of growth which is far in excess of the physiological, since they are about to die.

We know that every tissue which proliferates indefinitely contains zones of regeneration or germinal centres, in which alone mitoses are found and which are therefore responsible for growth and repair of physiological wear and tear. As regards the uterine epithelium, these are, according to Werth,[91] limited to the glands. I have myself seen them in curettings in the deeper segments of the glands and nowhere else. Although I admit that growth can take place by direct division of the nucleus, for a time at least, and that it can be succeeded by karyokinesis, it appears to me that it is unlikely that it will take place with blastomatous vigour in the absence of the only really vigorous cells of the tissue. It would seem as if these fragments were too superficial to contain them, but I cannot assert that this is really so. But we would not expect, upon the principle of self-preservation, that the germinal centres, in the absence of which repair must cease, would be destroyed or damaged during menstruation.

We ought not to drive a comparison between endometrial tumours and "implantation epidermoids" after cutaneous injuries for the following reasons: (1) The former are much more common than the latter. (2) The rate of growth of these approximates that of the skin (see Fig. 39 (IV)) and is not greatly in excess of the normal, as in our tumours. (3) The columnar basal cells of the skin, which represent its germinal zone, form a continuous layer and are therefore present in every fragment which comprises its whole thickness. If displacement alone predisposes for increased vigour of growth—one of the inevitable assumptions of Sampson's theory—we should expect traumatic epidermoids to be much commoner than they are. But they are rare, and it is exceedingly unlikely that fragments of menstrual endometrium which, at best, must be semi-necrotic, should, when transplanted, give rise to relatively enormous tumours. Sampson's statement that the ovary acts as an incubator need not be taken too seriously, since it is not supported by evidence.

Bailey,[4] a supporter of Sampson, and the latter as well, if I read him rightly, believe that whole fragments of endometrium, consisting of surface epithelium, tubules, and stroma with blood vessels, settle bodily upon the surface of the ovaries and proceed to establish themselves. Bailey figures these. His figures appear to me to refute his own arguments, since it is inconceivable that relatively large and complex pieces with an organoid structure should be vascularised with such

rapidity as to present no signs of necrosis. This is totally at variance with what we know of the behaviour of grafts of every kind, be they introduced into mice or men and be they cancerous or not. Sampson's theory is bound to fall in this form.

But Schindler [77] points out that all that is necessary for a successful graft to be established is that a single epithelial cell of the uterus should survive. Its descendents will, if they retain their uterine character, exert an influence upon the surrounding connective tissue which will compel it to assume the structure of the endometrium. This thesis is biologically and pathologically sound. I have no arguments to bring forward against it. But it remains to be proved that epithelial cells in menstrual fragments retain their vitality.

Lauche,[43] a convert to Sampson's theory, remarks that this can only be done in one of two ways: By tissue culture of menstrual fluid containing desquamated fragments and by experiments with menstruating apes. Tissue cultures have not as yet been attempted, to the best of my knowledge. Experiments have, however, been carried out upon a variety of animals, but they are beside the point, since they prove nothing that everyone was not prepared to admit. I mention those of Jacobson.[33, 34] In his first series, performed on rabbits, he produced intra-peritoneal nodules after autoplastic inoculation with fragments of uterine mucosa. They closely resembled cyst-adenomata. He claims to have demonstrated an increased vitality or " virulence " of these implants during œstrus. In his second series, with *Macacus rhesus*, he produced very typical intra-peritoneal islands of endometrium, which took part in menstruation. But, since he used curettings and not the fragments desquamated naturally at the menstrual period, his experiments teach us nothing we wish to know.

Sampson fails to explain why endometrial tumours should be confined to the lower half of the abdomen. If they are transplants there are no reasons that I can see why they should not " take " everywhere. Why are they never found upon the peritoneal surface of the diaphragm? We are told by physiologists that it is the great lymphatic drain of the abdominal cavity. I have noticed many a time that tubercles and secondary deposits are larger and more numerous here in cases of tuberculosis and malignant dissemination of the peritoneum than elsewhere, and Geipel [22] has shown that the patches of decidua in pregnancy are bigger here than on other parts of it. Gravity does not seem to produce much effect in these cases; then why should it be so active in endometrial tumours? *

* The assumption that tumours of laparotomy scars, when they are not connected with the uterus or associated with a ventri-fixation, are the result

I conclude that, although Sampson's theory cannot be disproved in the present state of our knowledge, it is based upon too many assumptions to be acceptable. And if I may venture a personal opinion, it seems to me to be much too easy and plausible to ring true. Many difficulties, which I cannot discuss here, are too readily met by modifying it to suit them. Nor does it account for extra-abdominal endometrial tumours,* except a part of those of laparotomy scars, and I have attempted to show, when dealing with these, that even here its assumptions are very far-fetched. To be quite candid, I do not like Sampson's theory, although I am far from denying its possibility and applicability in isolated cases.

(3) Peritoneal theory. Lauche,[41] in his first paper, tried to derive the epithelium of all endometrial tumours, with the exception of those of the mucosa of the uterus and Fallopian tubes, from the peritoneum. There is a good deal of evidence in favour of this view.

To begin with, the uterine epithelium is a derivative of the cœlom. The peritoneum can be shown to be present in every situation occupied by these tumours. Anatomical continuity has been established between the two in a number of instances.

If we take an epigenetic view of development and believe that normal differentiation, as I have argued above, depends upon a normal environment, which acts upon the potentialities possessed by the cells, there is no insuperable difficulty for the assumption that every differentiation which has taken place in the embryo can be repeated should the environment permit it at a future date. There are two provisos. The cells must not have lost the power to respond to its influence nor to divide and proliferate. But, since profound structural alterations do not take place in the cells of the body except by de-differentiation, which is always associated with division and proliferation, the problem is simplified. We must try to show that cells of the adult human body change their physiological characters—and not merely their outward form—in response to a pathological environment.

We get no help from general biology in our task, since this science, as generally practised, deals only with normal individuals. But these changes do not take place in the normal

of implantation of endometrium at a menstrual period is very far fetched. There is no positive evidence, but much presumptive negative evidence that the laparotomy was performed at a menstrual period. Once the wound is covered with granulations these would almost infallibly destroy a foreign body like an endometrial implant should it reach them.

* A minor objection this, since I hold no brief for single "explanations."

body. They are only found in pathological states as adaptations to an abnormal environment. Thus biologists, who know nothing of their existence, deny them in the higher animals, whereas in lower forms of life, which they are able to study by experimental methods, they proclaim that they are frequent and profound enough. It is the duty of pathologists to show biologists that they will never appreciate the adaptability displayed by the cells of the higher animals, which they can but rarely study with experimental methods, until they turn their attention to pathology.

There are many pathological lesions in all parts of the human body which are inexplicable except upon the assumption that a profound metamorphosis or "metaplasia" of the cells has taken place. As I have collected many instances from my own observation and the literature and discussed them in several publications (see [62, 63]), I need not go fully into them here. But one example need be given here. The heteromorphoses of the alimentary tract I was able to examine led me to these conclusions: Those that arise in development indicate that the prospective potencies of cells are wider than their prospective values. Those that arise in pathological states suggest that the original prospective potencies are not entirely lost in development, since they are sometimes accidentally revealed even in old age. How otherwise can one explain the presence of Brunner's glands in the gall bladder in a large proportion of cases of cholecystitis, or in tuberculous ulcers of the large intestine, or that of squamous epithelium in the gall bladder or pancreatic ducts? The only alternative explanation, the presence of a developmental anomaly, breaks down in many of these cases as elsewhere in pathology.

We are bound, or so it appears to me, to conclude upon the evidence that true metaplasia has been fully proved and established. I fail to see why it should not take place in the adult cells of the peritoneum when they are irritated and inflamed. There are no real reasons why these cells should not change their character and be converted into uterine epithelium. The great and at present insuperable difficulty is to define the change or changes of the environment that take place to make the metamorphosis possible.

Lauche [41] has shown that peritoneum is present everywhere where these tumours are found. They are in close relationship with it in the abdominal cavity. One of its diverticula, the canal of Nuck, is present in the inguinal region in development and persists in a number of cases, and herniæ are common here. The peri-umbilical fossettes investigated by Cullen [11] are by

no means infrequent at the umbilicus. The tumours of laparotomy scars are occasionally connected with the peritoneum or omentum (Meyer,[52] Klages,[40] Lauche,[41] Tobler,[87] Lemon and Mahle [47]) or with the uterus or another intra-peritoneal organ (Fraas,[19] Mahle and McCarty,[49] Lemon and Mahle,[47] Vassmer [88]), or shut off from the abdominal cavity by the peritoneum only (Lauche,[41] Lochrane [48]).

Histological continuity between the epithelium of the tumour and the peritoneum has been established by Hueter,[32] Lauche,[41] de Jong,[37] and Suzuki [84] on the intestines, by Chevassu [8] in the groin,* and by Tobler [87] in the umbilicus and a laparotomy scar. Although the number is small it is suggestive, since it is not to be expected that original connections are preserved in well-established tumours.

The only conclusion it is possible to reach is that there is no evidence in favour of dysontogenetic theories. Endometrial tumours are to be classed with the accidental or acquired malformations. Although there are difficulties for the acceptance of either of the remaining theories, these are smaller in the case of the peritoneal than in that of the implantation theory, since the assumptions that have to be made in the former are less numerous and better supported by general biological and pathological principles than in the latter.

The origin of the epithelium of endometrial tumours has been considered almost exclusively hitherto. It is necessary to discuss that of their cellular stroma and involuntary muscle briefly.

Biology teaches and pathology confirms that epithelium has a moulding or directing influence upon the subjacent connective tissue. This is not only true of normal development, but very obvious in most tumours and their metastases. I have discussed it in Study I (see Fig. 6 (I)). Epithelial tumours have a characteristic architecture, which often enables the morbid histologist to tell at a glance where they come from. None could be more characteristic than that of villous tumours of the bladder. Their epithelium rests upon delicate branched papillæ which consist of little more than wide capillary blood vessels and a few fibres of loose areolar tissue. This is also true of glandular carcinomata, which often mimic the structure of their tissue of origin with a surprising degree of accuracy. Unless their epithelium, in growing downwards into

* We have seen that the spaces described as lymphatic by Engelhardt,[17] Rosinski,[70] Szili,[85] and Emanuel [16] may have been peritoneal. Should this be so they should be added to this list.

the stroma, moulds the latter into a definite shape and induces it, so to speak, to assume a definite structure and consistency, it would be impossible for the characteristic architecture to be produced. We see the same thing in ulceration. When the epithelium begins to cover raw granulations, the configuration assumed by these varies in accordance with its type. If it be squamous they are soon converted into relatively non-cellular papillæ like the corium; if it be intestinal they are reduced to septa of cellular vascular stroma with numerous leucocytes. I have figured an excellent example of this in my paper on "Heteromorphoses," [62] Fig. 16. It represents a case of metaplasia of the epithelium of a polypus of the cervix uteri. Where the proliferating young epithelium is undergoing re-differentiation in the direction of cervical epithelium it rests upon a well-defined basement membrane; where it is squamous, this is absent. This specimen demonstrates clearly that the structure assumed by the stroma does not depend upon an inherited predisposition, a kind of *genius loci*, of its cells, since they were born and bred in the cervix uteri and have been always in contact with columnar cervical epithelium. This is shown even more clearly by metastases of carcinomata. In these the epithelial cells alone migrate to a distant part of the body. The stroma with which they are surrounded, and which is usually identical in structure and architectural arrangement with that of the primary growth, is entirely derived from the tissues of the new habitat.

Whatever be the origin of the epithelium of endometrial tumours, whether it be ultimately found in a congenital anomaly, in an implant from the uterine mucous membrane, or in a metaplasia of the peritoneal epithelium, the fact is firmly established by a multitude of writers, of whom I only mention Russell,[71] Goddard,[25] Cullen,[11] Sampson,[72-74], and Lauche,[41] that it is true uterine epithelium. And if, as I believe, the structure of the stroma of the endometrium of the uterus depends largely, if not wholly, upon the fact that it is in contact with uterine epithelium, there are no reasons, general or particular, why contact with the same epithelium should not result in the formation of true endometrial stroma in every part of the body in which it happens to take place.

The same line of reasoning can be applied to the involuntary muscle which is often present in these tumours, although I admit that, in doing this, we tread much more uncertain ground.

In those tumours which arise in or on the surface of muscular organs there are, of course, no difficulties, since the muscle is pre-formed. It is the musculature of the part that has under-

gone hypertrophy and sclerosis as a result of irritation. It is not even accommodated to the outlines of the ramifications of the endometrial tissues as a rule, but retains its original configuration and shape. It cannot be said to have entered into close enough relationship with the tissues of the tumour to be considered a part of them.

Involuntary muscle is occasionally present as sheets and bundles in tarry cysts of the ovaries (Fig. 91). They may attain a considerable thickness and be arranged around the cysts like *tunicæ propriæ*. But the ovary contains a few muscle fibres in its medulla (Schaffer [75]), which are independent of the blood vessels. We can assume that they have proliferated in response to the ectopic endometrial tissue and entered into a relationship with it which is comparable with that of the myometrium and the uterine mucosa.

But a number of cases is on record of the presence of plain muscle in endometrial tumours in parts of the body where this tissue does not occur naturally. It is present in at least nine tumours of the umbilicus and in about the same number in laparotomy scars. In the case of the latter the argument is brought forward, notably by Lauche,[41] that they are the result of implantation of uterine muscle at the operation. But this argument does not hold in other tumours of laparotomy scars or those of the umbilicus. Lauche,[41] who admits the directing influence of epithelium upon its stroma, does not feel justified in extending it to the more distant muscle, chiefly because the idea is not sanctioned by biology. I respect his caution. But I would inquire into the origin of involuntary muscle in development. It is not a tissue *sui generis*, which arises in certain localised areas in a distinctive way like skeletal muscle, but is formed, wherever this tissue is wanted, from mesenchyme cells which are histologically identical with their sisters. But how may we suppose that this happens? If we leave out the quasi-teleological factor in development, the apparent foreknowledge of what is to be,* which is so striking and impossible to explain, the differentiation of involuntary muscle must depend upon an external environmental factor. And is it not reasonable to try to find this factor in an influence exerted by the epithelium, or by it together with its stroma? How otherwise is it possible to visualise the *raison d'être* of the great differences between the muscular coat of the intestines and uterus?

* Since this factor appears to me to be universal in nature and equally pronounced in the simplest chemical reactions, and ought therefore to be accepted without argument.

I reiterate my belief that the things that have taken place in development will take place again in the adult organism, provided the environmental conditions be favourable. The endometrium leads its natural existence surrounded by a thick coat of muscle. Why should it not compel the neighbouring connective tissue cells to produce muscle in other parts of the body? What more natural than that it should hunger * for muscle and that, should it want it badly enough, it will get it? I can see no *a priori* reasons why it should not.

I admit freely and at once that these questions are not answered by pathology. I know of no evidence that involuntary muscle is produced *de novo* in pathological lesions. However, I have a good analogy in the ease with which cartilage and, more particularly, bone are produced around calcified necrotic areas in all parts of the body (see [62], where references to the literature will be found). There are few pathologists, I believe, who are prepared to deny that these tissues are formed by the activity of the inflammatory granulation tissue provided by the fibroblasts of the part.†

This finishes what I have to say about histiogenesis. Although these studies do not attempt to answer questions of ætiology, I would reiterate a few suggestive points.

Endometrial tumours are restricted to adult females. The fact that they are not found in the opposite sex is regarded as a mystery. And this it is. But it is no greater than, and will find its ultimate explanation in another—namely, that the uterine mucous membrane is not present in males. This is, therefore, not a pathological problem, but one for biologists and physiologists to solve.

These tumours are only found after puberty. It is within the province of pathology to ask the reasons why. Lauche [41] has the merit of having established that this must be due to the influence of the mature and sexually functioning ovary. I cannot here discuss his arguments, based upon sound biological reasoning, but would refer my readers to his paper.

The patients give a history of dysmenorrhœa or other disturbances of the organs of reproduction. Why this should be is obscure. Lauche's [41] argument that the tumour results

* An animistic figure of speech, perhaps, but one in frequent use in physiology.

† I may be accused by biologists, should these poor ruminations reach their notice, of riding the epigenetic theory of development to death, since my assumptions are often unsupported by biological dogma. *Ita.* But I might answer with the question: Are not certain parts of the biological edifice tottering to their fall *propter defectum reparationis*, and why should pathology not supply the materials for repair?

from a deficiency of uterine secretion cannot be supported, as pointed out by Meyer,[58] since hysterectomy in sexually mature women without removal of the ovaries should be followed by extensive endometrial tumours if this were true and should the peritoneal theory hold.

The topographical distribution of endometrial tumours deserves attention. Why are they restricted to the lower half of the cavity and wall of the abdomen?

The rôle played by inflammation, regeneration, and hyperplasia in the formation of these tumours is hotly debated. I have little doubt that here, as elsewhere in pathology, many "causes" are at work, in addition to the influence of the ovaries.

Conclusion

I have only "skimmed" the endometrial tumours in this paper, the weary length of which has dragged itself to rest. From the wealth of problems presented by them I have selected a few that are of peculiar interest for the morbid anatomist. Most of those that concern the general pathologist I have barely considered, not to mention those of purely gynæcological importance. I draw few conclusions, the chief being that these tumours are malformations and that they are acquired. I have, however, attained one object: I throw no light upon the causation of endometrial tumours. I am weary of the "explanations" so generally brought forward with assurance, since their authors deceive themselves and testify complete ignorance of the aims and methods of science. We pathologists have to suffer much from these delusions. Who could be more naïf than a recent writer, who trusts that "the pathology is now complete" with the advent of his paper? The word "explanation" in its scientific sense means no more—*nor* less—than that a sequence is *established*, and how often is this done to the satisfaction of even a single generation? When the difficulties that baffle us to-day are solved, the way will but be prepared for as yet undreamt-of problems. Du Bois-Reymond expressed this idea in his "*Ignorabimus*" speech. But this tense presumes a knowledge of the future possessed by no man. The scientific attitude is surely not to despair, but to look with hope into the future, and to express this hope in the words "*Ignoramus, semperne ignorabimus.*"

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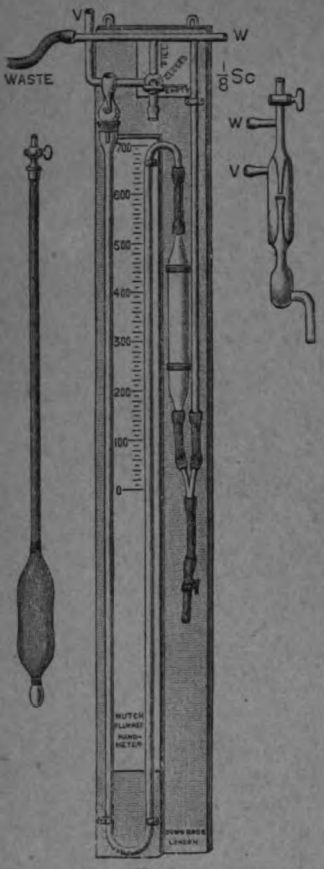

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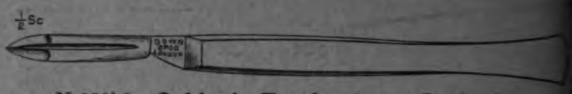

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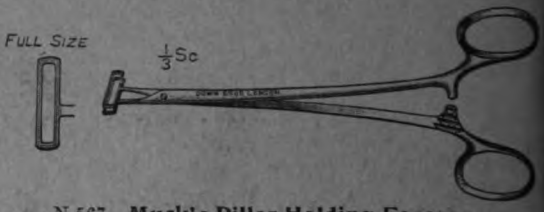

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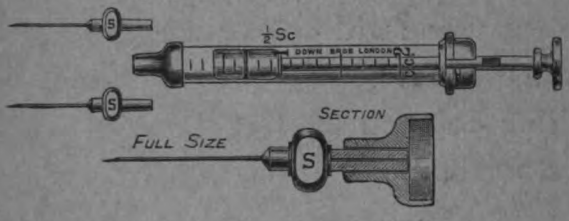

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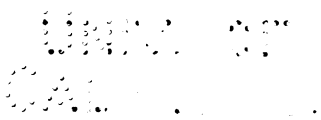
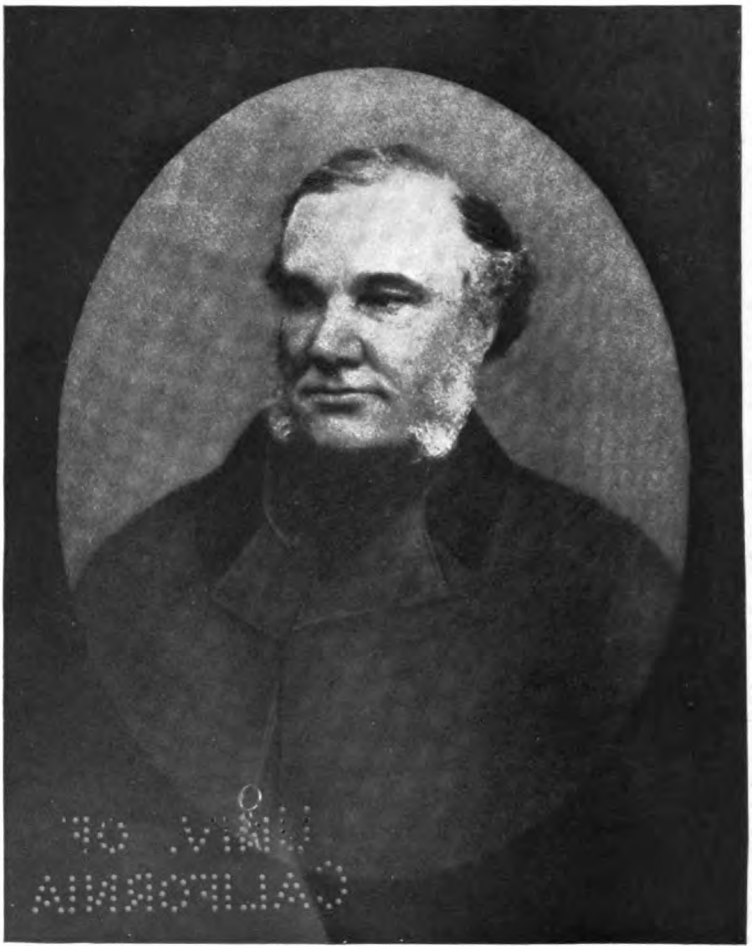




Thomas Addison

THOMAS ADDISON, M.D.

By Sir WILLIAM HALE-WHITE, K.B.E., M.D., Consulting Physician to Guy's Hospital.

Thomas Addison was born at Long Benton, near Newcastle-on-Tyne. Lonsdale * says that "the date of his birth is assigned to April 1793," and others, including the *Dictionary of National Biography*, give this year. Both the tablet in Guy's Hospital Chapel and that in Lanercost Abbey state that he died 29 June, 1860, aged 68 years. This arouses a suspicion that 1793 is not the date of his birth, for, if born April of that year, he would be 67 in June 1860, not 68 but only in his 68th year. The baptismal register of Long Benton Church has the following entry, for a photograph of which I am indebted to my friend Mr. Grey Turner: "1795, Oct. 11. Thomas s. of Joseph and Sarah Addison, Lg. Benton." The rector, the Rev. Mark Fletcher, has kindly supplied me with the following information which makes it very probable that Thomas was born that year. The baptismal register shows that on April 13, 1794, John the son of Joseph and Sarah Addison was baptised in Long Benton Church. Now it is very unlikely that, if Thomas was born in 1793, his baptism would be deferred till October 1795, his brother John being baptised between the birth and baptism of Thomas. The strong presumption is that Thomas was born in 1795, being therefore 65 years old, when he died in 1860, and that he was the second son, a view supported by the fact that Lonsdale says the brothers were John and Thomas, for he would put the elder first. It is easy to believe that in some transcription a 5 has become a 3.

The ancestors of these Addisons had lived for generations in the hamlet of Banks at "The Banks" or "Banks House," a stone's throw to the south of the Roman Wall in the parish of Lanercost, Cumberland. The house is high up on the right bank of the river Irthing, which, about half a mile away, separates Naworth Castle from the Priory of Lanercost. It faces south-west and has a wonderful view, the river, the Priory, and the trees surrounding Naworth in the foreground, and in the distance, Solway Firth, Skiddaw, Saddleback and Helvellyn. Other ancestors lived near, at St. Mary Holme, a house in the valley close to the river.

* Lonsdale: *The Worthies of Cumberland*, London, 1873, Vol. IV. p. 241.

The first Addison * mentioned in the documentary evidence of Lanercost is Sir Thomas Addison, who, in 1612, resisted payment of the customary dues to Lord William Howard of Naworth. In 1618 a Matthew Addison was convicted at Carlisle of horse-stealing, but was reprieved. In 1622 Edward Christopher Addyson was engaged in setting up the roof of the chapel (now the library) of Naworth Castle. From which of these Addisons, or Addysons, the physician was descended it is impossible to say, but in the Commonwealth Addisons were living both in Banks House and St. Mary Holme. The earliest of his ancestors we can clearly recognise is Thomas Addison, who

THE BANKS.

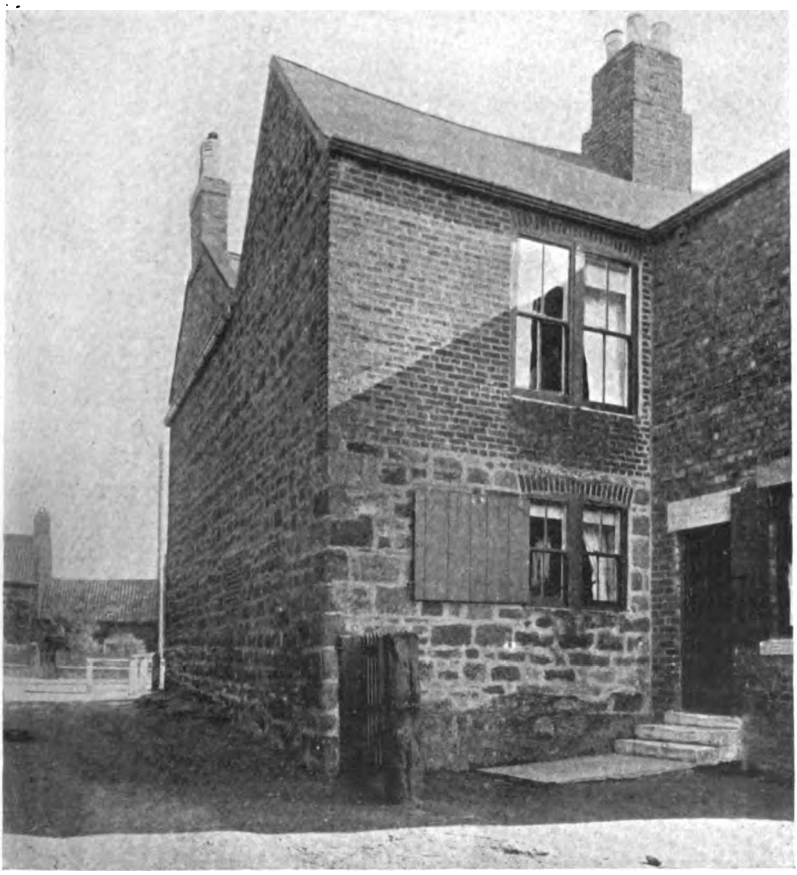
The ancestral home of the Addisons and where Thomas Addison, M.D., always spent his holidays. (From a photograph kindly supplied by Mr. G. E. Henderson.)

was born in 1636 and had Mary for his spouse. Their names come down to us on their oak chest, which still exists. On it is boldly carved the date 1676, the initials $\frac{A}{T.\ M.}$ and the inscription, "When God doth thee in store, remember thou the poor." This Thomas had a son, John Addison, who attained the age of 90; he had a son, Jonah, whose tombstone in Lanercost Church shows that he reached 84; one of his sons became a doctor, another, Joseph, became a farmer, and married Sarah Shaw, the daughter of a man who had a flour and grocery business at Long Benton. They had two sons, John and Thomas, the great physician. It appears that this married couple at one period lived at "The Banks," but Thomas was

* *Cumberland News*, October 15, 1920.

born at Long Benton, Joseph and Sarah presumably being there to look after the flour and grocery business. Joseph died in 1823 aged 67, and Sarah died at The Banks in 1841 aged 80.

The house in which Thomas was born is now a supply stores. The Rev. Mark Fletcher tells me that it is but little changed;



Back view of the house at Long Benton, in which Addison was born, as it appears to-day. The houses on the left are as they were when he was born. (From a photograph kindly supplied by Mr. Grey Turner.)

the several small panes of glass in the shop window have been replaced by a single large pane, the roof has been altered and a scullery has been built out at the back. Thomas Addison always looked upon himself as of Cumberland; when in London he went every autumn to The Banks for his holiday, and always said that he wished to be buried at Lanercost. His parents lived at Long Benton for some years; the elder son was born there, and Thomas was sent in the first instance to a school

kept by one John Rutter in a roadside cottage at Kellingworth, a little to the north of Long Benton, the same school in which Robert, the son of George Stephenson, was educated. From there he went to the Grammar School of Newcastle-on-Tyne, under the mastership of the Rev. Edward Moises; here he learned Latin so well that he was able later to take down lectures in that language and to speak and write it fluently. In answer to an inquiry from me, the present Head-Master, Mr. E. R. Thomas, kindly writes to say that no records of Addison's school career can be found save a Greek book with his name in it.*

His father wished him to follow law, but allowed his son to have his own way and study medicine, offering to make him a pupil of Dr. John Thomson of Edinburgh for three years, at an annual premium of £100 a year, but young Addison preferred to go straight to the University, where he entered as a medical student October 1812. Dr. J. D. Comrie has tried to trace his career there, but has gleaned little, except that Addison seems to have taken his courses in an unusual manner, for in his first winter the only University class he attended was that in chemistry; and in his first summer only that in midwifery. But in his second year he entered for classes in materia medica, practice of medicine, institutes of medicine, anatomy, botany, clinical medicine, clinical surgery and obstetrics. In his final year, 1814–15, he entered for clinical medicine, practical anatomy, chemistry and materia medica. He was never President of the Medical Society as stated by Lonsdale, nor did he distinguish himself specially when a student. On August 1, 1815, Thomas Addison graduated Doctor of Medicine, the subject of his thesis being *De Syphilide et Hydrargyro.*

It is generally supposed that he next visited some continental schools of medicine, but this is doubtful. Fortunately his father's means had been increased by the opening of collieries in his neighbourhood, so young Addison was able to try to make his way in London, where he had but one friend, a fellow-student who had lived in Edinburgh. He began by holding the office of House Surgeon to the Lock Hospital. When this appointment ended he first lived in Skinner Street, Snow Hill, in a haunted house; moving to Hatton Garden he became a pupil, and later on physician, at the General Dispensary, studying diseases of the skin under the celebrated Dr. Bateman. He was attached to this Dispensary for eight years, and on his retirement the Governors were so well pleased with him that they gave him a silver claret jug. He obtained the licentiateship

* For much help in learning about Addison's childhood I have to thank my friends Dr. Horsley Drummond and Mr. Grey Turner.

of the Royal College of Physicians on the 22nd December, 1819, and was elected a Fellow on the 4th July, 1838. He never became a Censor nor held any office at the College.

It is said that he began to study at Guy's Hospital about 1820. The correct date is 1817, for the books of the Guy's Medical School have this entry: "Dec. 13, 1817, from Edinburgh, T. Addison, M.D., paid £22 1*s*. to be a perpetual Physician's Pupil." There is another payment of £57 18*s*. from him to the School. What this was for we do not know. He soon attracted the notice of that beneficent despot, Mr. Harrison, the Treasurer, who did as much as any man for the good of Guy's, not the least of his benefactions being that, through his influence, Addison was appointed Assistant Physician on January 14, 1824, there being a vacancy consequent upon the promotion of Dr. Bright to be full physician because of the death of Dr. James Laird. Wilks says, "There were other candidates for the appointment, and amongst them, we belive, Dr. Seymour, well known for his good West End practice. He worked up great interest on his own behalf among Governors, and actually got a recommendation from the future King William IV. Showing the estimation in which Addison was held, Dr. Seymour sent his son some years afterwards to Guy's in order to study under his former rival." Mr. W. J. Curry has been good enough to supply me with the following extract from the Minute Book of the general Court of the Governors of Guy's Hospital:

"*January* 14, 1824.

"Mr. President requested to know if it were the pleasure of this Court now to proceed to the election of an Assistant Physician in the room of Dr. Bright, now appointed one of the Physicians to the Hospital.

"Resolved that this Court do now proceed to such election, whereupon the Petitions of Thomas Addison, M.D., John Burne, M.D., Thomas Cox, M.D., James Dunlop and Edward Seymour, M.D., were presented and read, respectively praying to be chosen such Assistant Physician, and they were severally called in whilst their petitions were read and then withdrew, after which it was represented by one of the Governors present that John Burne, M.D., Thomas Cox, M.D., and James Dunlop desired to withdraw their Petitions, and the same being withdrawn the Court proceeded by Ballot to chose an Assistant Physician, when it appeared that the Numbers were—

for Dr. Addison	38
for Dr. Seymour	6

whereupon Dr. Addison was declared to be duly elected Assistant Physician to this Hospital during the pleasure of a General

Court, and he was called in and acquainted with his election and the conditions thereof."

In 1827 Addison became lecturer on Materia Medica. In 1837 he was elected full physician, as the following extract shows:

"*August* 30, 1837.

"Mr. Treasurer informed the Court that the particular occasion of calling them together at the present time was to elect a Physician in the room of Dr. Cholmeley deceased, notice of which was entered in the summonses, and he requested to know if it is the pleasure of the Court to proceed to such election.

"Resolved, That this Court do now proceed to the election of a Physician in the room of Dr. Cholmeley, whereupon the petition of Thomas Addison, M.D., was presented praying to be chosen one of the Physicians of this Hospital, and he was called in whilst his petition was read. Mr. Treasurer inquired of Dr. Addison if he was informed as to the duties of the office and as to the relative situation of the Medical School in regard to the Hospital, and also that the regulation and management of the School were under the direction of the Treasurer? and he then withdrew.

"Resolved, That Dr. Addison be and is unanimously elected one of the Physicians of this Hospital during the pleasure of a General Court, and he was called in and acquainted with his election and the conditions thereof."

He was at the same time appointed joint lecturer on Medicine with Bright. In 1840, on Bright's retirement from the lectureship, Addison became sole lecturer and held this position until 1854 or 1855. During the years 1849 and 1850 he was President of the Royal Medico-Chirurgical Society.

In September 1847 he was married at Lanercost Church to Elizabeth Catherine, widow of W. W. Hauxwell, Esq., who had two children by her first marriage but none by that with Addison. She died in May 1872. In the Parish Register of marriages, neither Addison nor his wife give their age; both state that they are "of full age."

Generally his health was good, but towards the end of his life he suffered from gall-stones and jaundice. Early in 1860 he resigned his post of Physician to Guy's Hospital. So greatly did the students value his teaching, that a deputation of them waited upon him to urge him to withdraw his resignation, but he, poor man, knowing that he had a threatening disease of the brain, was compelled to persist. He had recently removed from Spring Gardens, where he had lived near Bransby Cooper's house for more than twenty years, to Berkeley Square, from

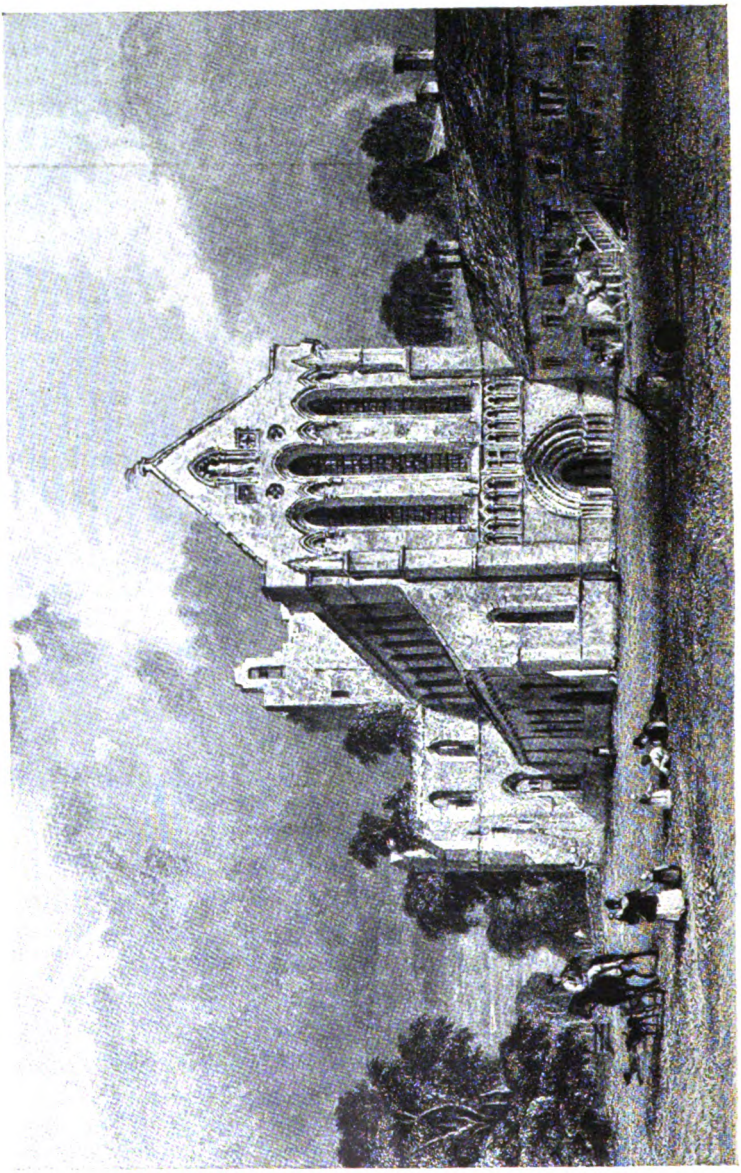
whence he went to Brighton for the benefit of his health. Here he died on June 29, 1860; he was buried under the old yew trees in the Abbey Churchyard, Lanercost, on July 5. For a time the tomb was neglected, but now the authorities of Guy's Hospital pay yearly to have it kept in order and clear of weeds. It is surrounded by the tombs of many Addisons. The parish registers * contain more than sixty entries under the name of Addison between the years 1731 and 1837.

The very beautiful Priory Church of St. Mary Magdalene, founded in the year 1169 by Robert de Vallibus † as an abbey for Austins or Black Canons, and at the dissolution granted to Thomas Dacre of Lanercost, stands near the river Irthing and is finely placed surrounded by wooded hills. With the conventual remains it has for centuries been known as "The Abbey," whilst the parish has been called colloquially and in episcopal registers "the parish of Abbey Lanercost." The part of the ancient buildings now used as a parish Church is the nave of the abbey. This and the surrounding ruins of the once magnificent abbey, with the green hills as a background, formed a peaceful picture when I saw them on a fine summer evening. A photograph of the Church and of Addison's tomb appeared in the *Guy's Hospital Gazette*, December 28, 1908.

The long epitaph from the tablet placed in Lanercost Church by his wife is printed in Lonsdale's book, where also will be found the words on the tablet in the gallery of the Chapel of Guy's Hospital, and those below his bust—for which a subscription among the profession was raised—in the hospital, where one of the medical wards was named after him and exists with the same name to-day. In the hall of the Counting House at Guy's there is a portrait of him; the front of the hospital forms the background and his hand is resting on a book, *The Practice of Medicine*. This picture was given by Mr. Jonathan Hutchinson to Mr. Clement Lucas for Guy's. Mr. Hutchinson, in a letter dated July 19, 1875, said that his brother bought it at an auction in Newcastle and that it was "by Bewick of Newcastle, whose life has, I believe, been recently written." The brothers Bewick of Newcastle were both wood engravers, not painters; one died in 1795, the other in

* *The Register of the Parish of Lanercost: Baptisms, Weddings and Burials*, 1731–1837. Edited by T. W. Willis, M.A., Beverley. Wright and Hoggard, Minster Press, 1912.

† *A Short Historical and Architectural Account of Lanercost*, a Priory of Black Canons, eight miles from Carlisle, upon the north side of the river Irthing, close to the Picts Wall, by Richard S. Ferguson and Charles J. Ferguson, London, Bell and Daldy, Carlisle, C. Thurnam & Sons, N.D.



LANERCOST PRIORY, CUMBERLAND.

From a print dated 1844. The churchyard in which Addison is buried is behind the wall on the left.

1828; neither worked in London. The portrait of Addison is that of a man of middle age, but in 1828 Addison was only about 33 years old; further, as the background is Guy's Hospital and neither of the brothers Bewick worked in London and neither was a painter, the portrait is not by either of the Bewicks of Newcastle. It is most likely the work of the portrait painter William Bewick,* sometimes said to be of Darlington, sometimes of Gateshead, who was born in 1795, died in 1866, worked much in London and also in Northumberland, and painted a great many portraits. Mr. Arthur Durham, who knew Addison, said this was a very good likeness. A stained glass window to his memory was placed in the east end of Long Benton Church and remained there till about thirty years ago, when it was removed to the south wall of the Church, where it is now the organ chamber window. There is no inscription on it and the figures have badly faded. His will, dated September 26, 1855, showed personalty under £60,000. The executors were his brother, John Addison of Banks House, and Alfred Brooke Barnes, surgeon, King's Road, Chelsea. To his wife he left his freehold estate and residence at Brighton, with its furniture, an annuity of £350 and his shares in the Indemnity Mutual Marine Assurance Company, and to her son and daughter an annuity of £100. His presentation plate was left to his brother to be kept as an heirloom.

Addison's † elder brother John left the Banks estate to John Joseph Addison, son of his cousin William Addison. From John Joseph it descended to Dr. Haygarth Maling Addison, whose brother sold it to Mr. G. E. Henderson, who now lives in Banks House. At the present time there is no Addison living in the neighbourhood.

On June 19, 1926, a meeting of the Border Counties Branch of the British Medical Association, in commemoration of Addison, was held at Lanercost, partly in the abbey, partly in the adjoining ancient Dacre Hall. It was very largely attended, doctors coming from as far as Edinburgh, Whitehaven and Newcastle; addresses were given by the Rev. A. P. Durrant, Dr. Norman Maclaren, Dr. J. D. Combie, and myself.‡

What kind of a man was he? The two best able to answer are Wilks,§ who was his pupil, and Lonsdale, his doctor friend

* Life and Letters of William Bewick, edited by Thomas Landseer, 2 Vols., London, 1871. In this book the names of very few of Bewick's sitters is given. Addison is not one of those named. That the portrait is by William Bewick is supported by the fact that Mr. Hutchinson, writing in 1875, speaks of Bewick's life as having been recently written, and this book was published in 1871.

† *Cumberland News, op. cit.*

‡ *The Carlisle Journal,* June 22, 1926; *Brit. Med. Journal,* June 26, 1926.

§ Wilks and Bettany: *Biographical History of Guy's Hospital,* London, 1892.

in Cumberland. The first tells us: "The personal power which he possessed was the secret of his position, much superior to what Bright could ever claim, and equal, if not greater, than that of Sir Astley Cooper. For many years he was the leading light of Guy's, so that every Guy's man during the thirty or forty years of his teaching was a disciple of Addison, holding his name in the greatest reverence, and regarding his authority as the best guide in the practice of the profession. . . He was dogmatic in his teaching, and thus the pupils accepted as pure gospel every word which flowed from his lips. The force of his words was enhanced by his mode of delivery and by the presence of the man himself. Addison was of good height and well made, stood erect, with coat buttoned up very high, over which hung his guard and eyeglass. He wore a black stock with scarcely visible shirt-collar, and this further elevated his head. He had a well-proportioned good head, with dark hair and side whiskers, large bushy eyebrows and smallish dark eyes, nose thick, as were also his lips, which enclosed his firmly knit mouth. His features were not refined, but belonged to a powerful mind, and showed no trace of any kind of sentiment. His penetrating glance seemed to look through you, and his whole demeanour was that of a leader of men, enhanced by his somewhat martial attitude." The students worshipped him, feared rather than loved him. He was melancholy and liable to fits of depression, and at times appeared haughty, unapproachable and even rude. Addison knew of this failing, by him said to be a cloak for his nervousness, which was such that he was all his life nervous when he began a lecture or address. But he could throw this off. When he was President of the Royal Medico-Chirurgical Society, he invited the reporters of the medical press to meet some of the leaders of the medical profession. "The evening was one of the most delightful I ever spent. Addison I had never met in private before; I had only known him as the great physician of Guy's Hospital, and the somewhat haughty and pompous President of two medical Societies, the Westminster and the Royal Medico-Chirurgical. I was astonished at his bonhomie, his hospitality, and his powers of conversation. . . . Foote joined me in eulogising Addison." * Wilks maintains that in reality he was an amiable man. "In his professional life no character on record has presented in a higher degree the sterling hard qualities of true professional honesty. We have never heard a single instance in which a word of disparagement of a professional brother escaped him." Lonsdale tells us how he loathed advertisement,

* J. F. Clarke: *Autobiographical Recollections of the Medical Profession*, London, 1874, p. 281.

indignantly refusing to write what he called "puffery," that he was musical, in politics a Tory, and considers that he would have risen to the top of any profession he had entered. He often did kindness by stealth, and the degree to which he was idolised by the students is shown by the fact that, when his health broke down, they sent him a letter of condolence; the touching answer from him, given in Lonsdale's book, reveals his deep affection for them.

We shall presently see that none of Addison's discoveries brought him fame in his lifetime. Nevertheless during it he enjoyed a very great reputation at Guy's, due entirely to his personal influence, to his surpassing power of teaching and to his clinical skill. That wonderful teacher, Astley Cooper, had retired from the hospital in 1825, so Addison reigned supreme. He even made the dry bones of Materia Medica attractive, for his fees derived from lectures on this subject were between £700 and £800 a year. Wilks says, "As a teacher, it is difficult to conceive a better. His lectures were of a very superior order, extempore, couched in good language, which amounted sometimes to real eloquence. The clinical lectures were most excellent . . . arguing both from positive and negative reasons, he placed the diagnosis on a sure foundation." Lonsdale writes: "Guy's Hospital had long had a deservedly high reputation, to which Sir Astley Cooper, Dr. Bright and others lent additional lustre; but some are of opinion that Addison, single-handed, raised a higher column than any of his predecessors of the present century. He was admitted to be one of the most impressive teachers of his day and assuredly popular among the students, many of whom were attracted to Guy's on his account alone."

In the third decade of last century there were dressers to the surgeons and clinical clerks to the physicians. The latter were taught to investigate patients in wards set apart for teaching. In 1828 Addison introduced the practice of making these clerks systematically write reports of the cases, and thus it is to him we owe the whole practice of clinical reports made by students. Always interested in them, he had a way of getting the best out of them, and instilling professional ardour into them. "Addison carried the pupils of Guy's as if by subtle traction." Great in himself, he strove to make others great, and he was always mindful of the fame of the school. Golding Bird dedicated his book on *Urinary Deposits* to him, saying, "It is now thirteen years since I found myself within the walls of Guy's Hospital, a stranger and unknown. In a short time my admiration and respect were excited for your profound

My opportunities of observing the
Conduct & pursuits of Dr. Golding
Bird have been unintermitted
from the period of his pupilage
to the present time. I have ever
regarded him as a most talented
& industrious student, his powers
of memory, & varied acquirements not
only in the various departments of
the profession but in every science
& branch of knowledge connected
with it. For some years past
Dr Bird has held distinguished
offices upon the
Staff of a large hospital, in
order, as I believe, to consummate
an Example of general, theoretical
& practical knowledge rarely
to be met with in a single
individual.

Thomas Addison M.D.
Senr Physician Westminster
& Guys Hospitals

24 Hill St. April 27. 1849

Reproduction of Testimonial given by Addison to Dr. Golding-Bird (see *Guy's Hospital Reports*, Vol. LXXVI. p. 11).
The original was kindly lent by Mr. C. H. Golding-Bird.

knowledge and experience as a physician and for your zeal as a teacher. But I soon experienced another feeling, that of gratitude for numerous acts of most disinterested friendship, for which I must ever remain your debtor."

After taking his degree, his chief interst was in diseases of the skin; this accorded with his work at the Lock Hospital, and at the Dispensary under Dr. Bateman. He always remained one of the best authorities in this department of medicine; it was he who superintended the making of the marvellous wax models of diseases of the skin that are the pride of the Guy's Museum, and at Guy's he used to give a course of demonstrations on cutaneous diseases during the summer session. But he was hostile to specialism; his mind was too great and his interest was too wide for him ever to be content with studying diseases of only a part of the body. He trained himself to take an infinitude of pains and to cultivate the art of exact observation; he was always at work either in the wards or the dead-house, and so attained an enormous experience, on which he relied far more than on book knowledge; he had the supreme gift, not only of acquiring all the possible evidence about a case, but of using it with great judgment, unerringly separating that which was relevant from that which was not. All this, together with his exceptional sagacity, gave him the reputation of being the most skilful man of his day in unravelling a difficult case, and the reputation was deserved. He seemed to search deep into the innermost parts of the human body, much as a man would try to discover the derangement of a complicated machine, and he appeared literally to drag the malady to light. No time was too long for the investigation of a case; he must solve the problem. He was accustomed to say that, when returning from a hospital or private patient, he revolved in his mind every possible condition to account for the symptoms. Once in the middle of the night and to the astonishment of the Sister he appeared in the Clinical ward, because when he got into bed at home, he remembered that he had not satisfied himself that a patient, whom he had seen in the afternoon, had not got a hernia. Naturally such a man compelled himself to be an accomplished auscultator; being this, he was aware of the difficulties of the subject. Nevertheless the audience were surprised when, in a paper read before the Physical Society on February 28, 1846, *On the Difficulties and Fallacies attending Physical Diagnosis of Diseases of the Chest,* he enumerated forty-two difficulties and fallacies, but his doing so was characteristic of his carefulness and thoroughness.

Some blamed him because, having made a diagnosis, he did

not always prescribe for the patient, but this, as Lonsdale says, arose from the best of motives, for often Addison, being honest, had to admit that he did not know any drug which would be of benefit. He did not belong to that class who always must do something; he was wise enough to be aware that Nature can do much unaided, that when we do not know of a remedy, it is more just to ourselves and better for the patient not to give one, for it may do more harm than good.

Great as was Addison's reputation amongst those whose approbation was alone worth having, namely, those of his own profession who knew him, he was not successful in building up a large practice, and he was almost unknown to the general public. So much the better for the science of medicine, for he was left free to teach and to make his discoveries. Still, one fact connected with private practice is worth recording. He was called to see a member of the Rothschild family in Paris. Trousseau, Nelaton, and all the élite of the profession in that city attended a public dinner in his honour. His health was proposed, and Addison replied in excellent French. Truly a prophet is not without honour save in his own country.

No man has ever been held in greater esteem at Guy's than Addison. Yet, because he was of a retiring, somewhat forbidding nature, the medical public in England, outside those with whom he was in immediate contact, paid little attention to him or to his discoveries in his lifetime. Neither the *Lancet* nor *British Medical Journal* published an obituary notice of him when he died, the College of Physicians did not elect him as a Fellow till nineteen years after he had become a Licentiate, he never lectured or held any office at the College, his name never appeared among the list of candidates for the fellowship of the Royal Society, no University gave him an honorary degree, he held no Court appointment, he was not a member of the newly-formed Pathological Society, and the Royal Medico-Chirurgical Society refused to publish some of his papers, even after he had been President of it.

Now his fame is world-wide, for not only was he a great personality, a brilliant teacher and an exceptionally skilful diagnostician, but he made fundamental discoveries in several departments of medicine. The writer of the obituary notice of Addison in the *Medical Times and Gazette*,* the only medical paper that thought it worth while to notice the great man's death, put his work on pneumonia and phthisis first in importance, and Wilks did also. Addison's teaching on these and other subjects is now so completely the familiar

* *Medical Times and Gazette*, July 7, 1860.

knowledge of every student that it is difficult to imagine ourselves without it. As nobody can precisely gauge the relative value of discoveries, I will take Addison's in the order in which he published them, and will give extracts from his writings * to show that he was the first—

(1) to teach what clinical signs are presented by a patient with a fatty liver;
(2) to give an account of the symptoms and post-mortem appearances of appendicitis;
(3) to demonstrate that pneumonia is not an inflammation of the parenchyma of the lung, for that does not exist, but that its morbid anatomy consists of an inflammatory exudate into the air cells; also that carnification of the lung is due to pressure by pleural effusion;
(4) to demonstrate that tubercles are not the sole cause of the change in the lung in phthisis, but that ordinary inflammation contributes—in other words, phthisis is a mixed infection;
(5) to point out that vitiligoidea or xanthoma, of which he gave an original description, is associated with jaundice;
(6) to discover the existence of Addison's anæmia, often called pernicious anæmia, and to give a perfect clinical description of it;
(7) to discover the existence of Addison's disease, to give a perfect clinical description of it, to assign it to destruction of the supra-renal capsules, and thus to lay the foundation of modern endocrinology.

Fatty Liver.

The post-mortem appearances of a fatty liver and its association with phthisis were well known before Addison's time, but medical authors bewailed their complete ignorance of any clinical symptoms, which would enable them to predict that a fatty liver was present. Characteristically Addison applied himself to the problem, and published a paper,† in which he said that as a result of his observations he considered that a fatty liver might be predicted during life if " to the eye the skin presents a bloodless, almost semi-transparent and waxy

* There are in the Museum of Guy's Hospital many water-colour drawings which Addison had done to illustrate his discoveries. They are mostly by William Hurst; the execution is most beautiful. A few are by his colleague, John Lucas Tupper, the pre-Raphælite artist.

† " Observations on Fatty Degeneration of the Liver," by Thomas Addison, M.D., *Guy's Hospital Reports*, 1836, Vol. I. p. 476.

appearance; when this is associated with mere pallor, it is not unlike fine polished ivory; but when combined with a more sallow tinge, as is now and then the case, it more resembles a common wax model. To the touch, the general integument, for the most part, feels smooth, loose and often flabby; whilst in some well-marked cases all its natural asperities would appear to be obliterated, and it becomes so exquisitely smooth and soft as to convey a sensation resembling that experienced on handling a piece of the softest satin." All subsequent physicians have confirmed the accuracy of this entirely original observation, which could only have been made for the first time by one endowed with an altogether exceptional gift for seeing. Addison tells us that the above condition of the skin is first to be noticed on the face and the backs of the hands. He gives cases in which he correctly foretold a fatty liver from the aspect of the skin, and he remarks that a fatty liver may have other causes than phthisis, one of which is alcoholism. The paper is illustrated with a beautiful chromolithograph of a fatty liver.

Appendicitis.

In 1839 there was published the *Elements of Practical Medicine*, by Richard Bright, M.D., and Thomas Addison, M.D., Physicians to Guy's Hospital and Lecturers on the Practice of Medicine. Only Vol. I ever appeared; hence, as the book is incomplete, it is rare. In the Preface the authors state that they have felt the want of an elementary and practical book, to which they could refer their pupils, and that in this work they have endeavoured "to state, with as much conciseness as is consistent with perspicuity, the history, symptoms and treatment of each disease, as established in their own minds, by what they have read as well as by what they have seen." The result is admirable; the *Elements* are just what a text-book should be, not a conglomeration of what this or that person has said, but a plain statement in excellent English of the experience of two great teachers.

From what I have read and from what I have heard said by my teachers, the general opinion was that most of this first volume was written by Addison, so that almost certainly he is responsible for what I am going to quote, and at any rate he is jointly responsible for the first accurate account of appendicitis. No reference to this occurs in the first six modern text-books I took up by chance, and Deaver * in his very full history of the disease does not mention it, but Kelly † does in these words:

* Deaver: *A Treatise on Appendicitis*, 1900.
† Kelly: *Appendicitis*, 1909.

"descriptions so clear and well presented that they could not be surpassed to-day."

On page 498 of the *Elements*, under the heading "Inflammation of the Cæcum and Appendix Vermiformis," we find the following: "The history of this affection is often as follows:—The patient has complained, more or less, for some time past, of pain and uneasiness in this part, increased on exertion, or after neglect of the bowels, or excess in eating or drinking; he has, however, retained such a share of health that he has not been interrupted in his daily avocations, till, after some unusual exposure to cold, or some long walk, or other over-exertion, he has been suddenly seized with more severe pain, attended with rigors, chills, and sometimes with sickness and violent vomiting. The pain and tenderness become excessive, and extend to the neighbouring parts of the abdomen. A hardness and tumefaction are soon very evident to the hand in the part first affected: this continuing, general symptoms of peritonitis often take place, and terminate fatally; but under careful treatment the inflammation remains circumscribed, and becomes even less extensive, assuming the form of a local, deep-seated abscess. The threatening symptoms of peritonitis subside; the tumefaction just above the crest of the ilium on the right side is more and more obvious to the touch, and gradually shows a tendency to point; the constitution still suffering severely. In process of time it either opens of its own accord, or is assisted by the lancet, and a discharge of ill-conditioned pus follows, which from its peculiar fetid smell, and from its appearance, is soon discovered to be mingled with feculent matter. The discharge continues for many weeks and the patient often sinks at length from exhaustion. In other cases, when the powers of the system are previously unbroken, the abscess closes and permanent recovery is obtained.

"*Morbid appearances.*—From numerous dissections it is proved that the fæcal abscess thus formed in the right iliac region arises, in a large majority of cases, from disease set up in the appendix cæci. It is found that this organ is very subject to inflammation, to ulceration, and even to gangrene . . . this little worm-like body is often detected in the midst of the abscess, with a perforation at its extremity; or by ulceration higher up in its parietes; a considerable portion of it, nearly or entirely separated, is found in a disorganised condition among the pus and fæces which fill the abscess . . . it sometimes points at a considerable distance from the original source of the disease."

About thirty years ago the profession thought that some of

its members had discovered appendicitis; they discussed whether it was a new disease, but Addison had given a perfect description of it before most of the supposed discoverers were born.

Diseases of the Lungs.

Addison devoted more attention to diseases of the lungs than to any other branch of medicine. The collection of his published works * contains five papers bearing on this subject. Readers of his writings will see that he had the greatest reverence and admiration for Laennec; he acknowledged "himself indebted for almost all he knows of thoracic diseases to that truly great man, at once the most distinguished and most successful cultivator of medical science that ever adorned the profession." Nevertheless, in two important matters, namely, pneumonia and phthisis, his teaching differed from that of Laennec.

Before Addison's time it was universally believed that pneumonia consisted of an exudate into the interstitial structure of the lungs. It was defined by Laennec as "inflammation of the lung tissue." † Opinions as to the structure of the lungs were variable and inaccurate. Addison made matters plain; he wrote: "Accompanied by a corresponding branch of the pulmonary artery, I trace a filiform bronchial tube to a lobule or bunch of (air) cells, in which it abruptly terminates; the blood distributed over these cells being received by the pulmonary veins, which pass exteriorly to the air cells, in a loose and very distinct interlobular cellular tissue. I entirely fail to discover any structure to which the term interstitial or parenchyma can be fairly applied." This quotation is from a paper read before the Guy's Physical Society in 1843,‡ and is a condensed statement, the details of which he had previously published § and had often mentioned when teaching orally. On the same occasion (1843) he reiterated his earlier announced views on pneumonia thus: "There are probably some present who remember the time and occasion when, in this Society, and in opposition to all existing authorities, I ventured to call into question the long-cherished notion that pneumonia had its seat in a supposed parenchyma of the lungs and that the

* *A Collection of the Published Writings of the late Thomas Addison, M.D.*; by Dr. Wilks and Dr. Daldy. The New Sydenham Society, London, 1867.

† *De l'Auscultation Médiate*, by Théophile H. Laennec. First edition, Paris, 1819.

‡ "Observations on Pneumonia and its Consequences," *Guy's Hospital Reports*, 1843, Vol. VIII. p. 365.

§ "Observations on the Anatomy of the Lungs," *Trans. Royal Medical and Chirurgical Society*, 1840.

products of pneumonic inflammation were poured into that parenchyma." The occasion to which he refers was in 1837, when before the same Society he said: "I entertain no doubt whatever of its (pneumonic inflammation) being primarily and essentially seated in the (air) cells themselves," * and his discovery can be best briefly expressed by a few words taken from the work by Bright and himself.† "Pneumonia may be defined to be an inflammation of the air cells of the lungs, speedily producing an effusion into them of a serous-looking fluid commonly mixed with blood; causing, if unchecked, such a degree of thickening of their parietes as apparently to fill them up entirely for a time; or leading to the deposition of an albuminous matter, which is either solid or of a puriform character; and seldom, if ever, terminating in the formation of a genuine abscess." There follows an admirable detailed description of the stages of engorgement, red hepatisation and grey hepatisation. Addison, as a result of careful dissection of healthy lungs, had given an accurate and correct account of the minute anatomy of the lungs, and, by diligent examination after death of the lungs of those afflicted with pneumonia, he was able to show that the universal opinion as to its morbid anatomy was entirely wrong, and he was able to describe the morbid anatomy with an accuracy which no one has since challenged. He insisted that the same morbid anatomy is true of lobular pneumonia. He alluded to the condition of lung described by Laennec as carnification and regarded by him as the result of pneumonic inflammation modified by pleural effusion. Addison demonstrates that this is not so, that the whole condition of carnification is due to compression by fluid, and that inflammation plays no part.

In his clinical description of pneumonia he lays much emphasis on his experience that cough and expectoration may be entirely absent. He also says, "But of all the symptoms of pneumonia, the most constant and conclusive, in a diagnostic point of view, is a pungent heat of surface." It is difficult to say who is the first to observe a symptom, but certainly this one was not generally known before Addison's time. To show how slowly his original and correct teaching spread, a reviewer of Dr. Barlow's *Manual of Medicine* in 1856 said, "Dr. Barlow defines pneumonia to be an inflammation of the air cells of the lungs, a definition not

* "Observations on the Diagnosis of Pneumonia," *Guy's Hospital Reports*, 1837, Vol. II. p. 57.

† *Elements of the Practice of Medicine*, by Richard Bright, M.D., and Thomas Addison, M.D., Vol. I., London, 1839.

only calculated to give erroneous ideas to the student, but certainly not correct. True pneumonia nearly all authorities, we thought, were now agreed in regarding as an inflammation of the interstitial tissue or parenchyma of the lungs."

Turning now to phthisis, Laennec, it is true, admitted that pneumonic consolidation may occasionally be found in persons dead of phthisis,* but he did not lay stress on this, nor did he think it common. The cavities and most of the features usually seen in the lungs of phthisical patients were in his opinion due to the softening of, or the presence of, tuberculous matter. Addison disagreed, and taught that most of the changes seen in a phthisical lung are due to pneumonic inflammation. Thus the last words in his article "On the Pathology of Phthisis" † are: "inflammation constitutes the great instrument of destruction in every form of phthisis." In the same communication he says, "I very much question whether there ever was a single instance of tubercular disease of the lung proving fatal, in which more or less of this pneumonic change might not have been distinctly recognised, if the prevailing notions respecting tubercular infiltration had not obscured the perception of the beholder." He tells us that the inflammatory products may contract, leading to a diminution in the size of the lung and flattening of the ribs; this contraction, he says, is a favourable sign in every form of phthisis, for it indicates an attempt at repair, or they may lead to mere induration, which in some cases is also a stage towards repair, or they may break down to form a cavity.

Those who read Addison's "Pathology of Phthisis" nowadays may be inclined to urge that he under-estimates the importance of the tubercles, for he maintains that in some forms of phthisis no tubercles can be found, but this criticism is hardly fair, because nearly all his work was done by observation of the naked-eye morbid anatomy of the lung; microscopy was then in its infancy and tubercle bacilli had not been discovered. What he did was to enunciate that in phthisis there are two processes at work, the tubercles and ordinary inflammation. This was an immense step forward, and although his work dates back more than eighty years, it is the same as is taught to-day, for, while we now know that in all cases of phthisis tubercle bacilli have been at work, we also know that in nearly every case other organisms are also present and that they are responsible for many of the symptoms and for much of

* Laennec: *Selected Passages from De l'Auscultation Médiate*, translated, with a Biography, by William Hale-White, Part I. chap. ii. Art. I. London, 1923.

† "On the Pathology of Phthisis," *Guy's Hospital Reports*, 1845, Vol. X. p. 1.

pulmonary change. Addison's teaching, translated into modern terminology, was that in every case of phthisis there is a mixed infection. But this entirely original and revolutionary doctrine spread very slowly, for when in 1870 Baumler translated Niemeyer's *Clinical Lectures on Pulmonary Consumption*, second edition, 1867, into English, for the Sydenham Society, he said, "The views insisted on by Professor Niemeyer have almost to their whole extent been confirmed by the results of recent investigations. But the renewed study of the whole question has led also to more just appreciation of the works of former observers. In this country the labours of Thomas Addison, which had almost been forgotten, and which had remained almost entirely unknown on the Continent, have been brought to light again, and show that already, at a period when Laennec's teaching had just commenced to dominate over the pathology of lung diseases, an independent observer arrived at and firmly held the opinion which in more recent times was established by Reinhardt, Virchow, and his disciples, and which forms the key-note of these lectures—namely, that, to use Addison's own words, 'inflammation constitutes the great instrument of destruction in every form of phthisis.'" In Niemeyer's lectures themselves there is no reference to Addison or to his teaching. The reviewer * of the translation notes this and says, "Dr. Baumler has done justice to our countryman, Dr. Thomas Addison," and previously the *British and Foreign Medico-Chirurgical Review*, in reviewing Niemeyer's work in 1870 said, "Dr. Addison perhaps did more than anyone else in England to advance the doctrine of 'pneumonic phthisis.'"

Vitiligoidea (*Xanthoma*).

A paper entitled "On a Certain Affection of the Skin, Vitiligoidea—Plana, Tuberosa" was published by Addison and Gull.† It is almost certainly chiefly by Addison, for he was then senior physician; Gull was the junior assistant physician. Some of the cases described were Addison's patients; I cannot trace that any were under Gull, and Wilks and Daldy ‡ state that Addison was the first to describe Vitiligoidea. This disease became known later as Xanthalasma and is now called Xanthoma. Whether the flat and the tuberose form are distinct entities or varieties of the same condition has been disputed. Be this as it may, the plane variety is the commoner, and, as the

* *British and Foreign Medico-Chirurgical Review*, April 1871.
† *Guy's Hospital Reports*, Series 2, Vol. VII. Part 2, p. 265.
‡ *A Collection of the Published Writings of the late Thomas Addison, M.D.*, New Sydenham Society, 1868.

authors noted, is often associated with chronic jaundice, and usually appears most evidently on the eyelids as patches of a light opaque colour with the surface and edges slightly raised. There is no doubt this paper is entirely original and constitutes the first description of a definite clinical entity.

Addison's Disease and Addison's Anæmia.

Only once has a physician achieved the distinction of discovering two diseases, and of having them both named after him, and that physician was Addison.

The story is as follows :—On March 15, 1849, at a meeting of the South London Medical Society, John Hilton, Addison's colleague, being in the chair, he read a paper * on what he described as a "remarkable form of anæmia," whose approach is indicated by languor and restlessness; next follow pallor and loss of strength and enfeeblement of pulse; all these symptoms progress, shortness of breath succeeds, and "the whole surface bears some relation to a bad wax figure." The patient dies from sheer weakness, not from wasting. In only three cases was there an inspection after death, and in all of them a diseased condition of the supra-renal capsules was found. The author had a strong impression that the disease of the supra-renals was the cause of the malady, "at all events he felt the time had come for directing the attention of the profession to these facts." It will be noticed that there is no mention of pigmentation nor of vomiting in this preliminary communication, which, however, is of great historical importance, for in it is the first evidence that the supra-renals are essential to life, and the whole of endocrinology dates from March 15, 1849.

Addison continued to work at the subject; he got Wilks, then a young man about the hospital, to collect cases, and in 1855 he published the famous thin book, illustrated with chromolithographs, entitled, *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules.*† In the preface he remarks that occasionally the pathologist may be able to give a more decisive reply as to the function of an organ than the physiologist, and that pathology and physiology mutually advance and illustrate each other. Addison puts forward his book as a "first and feeble step" in the inquiry as to the functions of the supra-renal capsules.

After a few preliminary sentences, the author, "as a preface

* *Medical Gazette*, March 23, 1849, pp. 517 and 562.

† *On the Constitutional and Local Effects of Disease of the Supra-renal Capsules*, by Thomas Addison, M.D., Senior Physician to Guy's Hospital, London, Churchill 4to, pp. 39, with Coloured Plates, 1855.

to my subject," announces the discovery of a new disease, that which is now universally known as "idiopathic anæmia," "pernicious anæmia," or "Addison's anæmia." He says that for a long period he had observed a remarkable general anæmia, which had no discoverable cause, which he was accustomed to call "idiopathic." "It makes its approach in so slow and insidious a manner that the patient can hardly fix a date to his earliest feeling of that languor which is shortly to become so extreme. The countenance gets pale, the whites of the eyes become pearly, the general frame flabby rather than wasted; the pulse perhaps large, but remarkably soft and compressible . . . there is an increasing indisposition to exertion, with an uncomfortable feeling of faintness or breathlessness on attempting it; the heart is readily made to palpitate; the whole surface of the body presents a blanched, smooth and waxy appearance; the lips, gums and tongue seem bloodless; the appetite fails; extreme languor and faintness supervene, breathlessness and palpitations being produced by the most trifling exertion or emotion; some slight œdema is probably perceived about the ankles; the debility becomes extreme. The patient can no longer rise from his bed, the mind occasionally wanders, he falls into a prostrate and half-torpid state, and at length expires. Nevertheless, to the very last, and after a sickness of perhaps several months' duration, the bulkiness of the general frame and the obesity often present a most striking contrast to the failure and exhaustion observable in every other respect.

"With perhaps a single exception the disease . . . sooner or later terminated fatally. . . . After death I have failed to discover any organic lesion that could properly or reasonably be assigned as an adequate cause of such serious consequences."

Whilst seeking to throw light on this disease, Addison, to use his own words, "stumbled upon" another malady, now universally known as "Addison's disease," but which he called either "Bronzed skin" or "Melasma Suprarenale." He begins thus:—"The leading and characteristic features of the morbid state to which I would direct attention are, anæmia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, a peculiar change of colour of the skin, occurring in connection with a diseased condition of the supra-renal capsules." Then follows a perfect description of the languor, feebleness of pulse, occasional vomiting, weakness, pigmentation of the skin and lips, all foreshadowing a fatal termination without at any time any physical signs. The cases are given in detail; the first four are

undoubted examples of the disorder and are those on which Addison founds his discovery; the fifth he quotes from Bright, who had observed the cutaneous discoloration and other symptoms, and had noticed the diseased condition of the suprarenals shown after death, but he was unaware of the connection between this and the symptoms. There are six others given; Addison evidently regarded these as doubtful, and I think most readers would agree that they are not examples of the disease in question.

This thin quarto book of less than forty pages of large print, and mostly occupied with reports of individual cases, thus contains the first description of two diseases now known all over the world. Addison's account of each is so perfect that nothing has been found wrong in his clinical picture, and nothing has been added except facts that have been obtained by instruments which he did not possess, and a few occasional symptoms not present in the cases he described.

There was no review of this book in the *British Medical Journal*. That in the *Lancet* * was half-hearted and rather foolish, the reviewer not understanding that two diseases were described. That in the *Medical Times and Gazette* † warmly praised it, saying, "We believe that Dr. Addison has made a discovery which is one of the most important practical medicine has produced for many years, and one in every way worthy of the untiring zeal and energy in professional pursuits which have characterised his life."

It took a long while to convince people of the reality of Addison's anæmia. This was partly because he called it "idiopathic," and partly because later writers called it "pernicious anæmia." Two worse adjectives could not have been found, for any anæmia of which the cause was not evident was called idiopathic, and any severe case was naturally called pernicious. As recently as 1887 ‡ its existence was denied, but now it is universally recognised as a distinct malady, and further confusion will be avoided if it is called "Addison's anæmia." Addison's successors at Guy's have contributed considerably to the proof that Addison discovered in this form of anæmia a new disease; Wilks,§ Pye-Smith ‖ F. Taylor,¶ Hale-White,** H. French †† and J. M. H. Campbell and J. J. Conybeare ‡‡ have recorded many additional cases. Occasional symptoms, not

* *Lancet*, October 27, 1855.
† *Medical Times and Gazette*, February 9, 1856.
‡ G. F. P. Henry: *Anæmia*, Philadelphia, 1887.
§ *Guy's Hospital Reports*, Vols. XVIII. and XX.
‖ *Ibid.*, Vol. XLI.
¶ *Ibid.*, Vol. XXXVIII.
** *Ibid.*, Vol. XLVII.
†† *Ibid.*, Vol. LIII.
‡‡ *Ibid.*, Vol. LXXII.

present in Addison's original description, have been added by these writers, such as the rare pigmentation in the mouth, the slight pyrexia, the occasional retinal hæmorrhages and those of gastro-intestinal irritation. F. G. Hopkins * has dealt with the question of free iron in the liver and the state of the blood; the changes in the nervous system, and the quality of the gastric secretion, which has particularly engaged the attention of Hurst, Ryle and Bennett, have all been studied. † ‡

Although Greenhow, in his Croonian Lectures on Addison's disease delivered before the Royal College of Physicians twenty years after the publication of Addison's discovery, thought that the knowledge of it had spread slowly, there is no doubt the profession acknowledged the truth that a new disease had been found much more quickly in this case than in that of Addison's anæmia. It is true that many denied its existence, but Trousseau quickly appreciated the discovery and named the malady Addison's disease, by which designation it has since always been known. Quite soon after 1855 cases of it were reported in the medical journals. Wilks § wrote on the history of it, and those who succeeded Addison at Guy's and recorded cases in the *Reports* were Wilks,‖ Habershon,¶ T. Wilson-Smith ** and Conybeare and Millis.†† Although a rare malady, Addison's disease has passed into general literature. Readers of Wendell Holmes' *Poet at the Breakfast Table* will remember that the poet consults Dr. Franklin for a discoloration on the forehead.

"'The colour reminds me,' said Dr. Franklin, 'of what I have seen in a case of Addison's Disease, Morbus Addisonii.'

"I said I thought the author of the *Spectator* was afflicted with a dropsy to which persons of sedentary and bibacious habits are liable!

"'The author of the *Spectator!*' cried out Dr. Franklin; 'I mean the celebrated Dr. Addison, the inventor, I would say, discoverer, of the wonderful new disease called after him!'"

Addison's other publications were few and of far less importance. The only clinical lecture we have is one *On the Disorders of Females connected with Uterine Irritation*. This was published by request in pamphlet form in 1830. The argument is that many women suffer from various nervous and hysterical affections, from indigestion, flatulence and vomiting, and particularly from pains about the body, especially under the

* *Guy's Hospital Reports*, Vol. L.
‡ *Ibid.*, Vol. LXXIII.
‖ *Ibid.*, Vol. XX., Vol. XXIII., Vol. XXVI.
** *Ibid.*, Vol. LIV.
† *Ibid.*, Vol. LXXII.
§ *Ibid.*, Vol. XXXVII.
¶ *Ibid.*, Vol XXV.
†† *Ibid.*, Vol. LXXV.

left breast, but that they are wrongly and harmfully treated by severe local treatment when really the cause which ought to be treated is uterine irritation, which is manifested by irregular, painful menstruation, tenderness of the womb and leucorrhœa. The lecture is full of good observation of many cases. It is clear that the speaker felt strongly about the unnecessary suffering that followed incorrect treatment.

In 1846 he read before the Guy's Physical Society a paper, published in the *Guy's Hospital Reports* of the same year, "On the Difficulties and Fallacies attending Physical Diagnosis in Diseases of the Chest." He begins with a fine eulogy of Laennec. He then tells us that many who pretend to use the stethoscope properly cannot interpret what they hear, and, even if they hear correctly, do not know the value of that which they have ascertained, and lastly that there are many who rely too exclusively on the stethoscope, paying little attention to any other evidence than such as is afforded by it. The bulk of the communication consists of forty-two propositions, mostly illustrated by cases, and each enunciating a difficulty or fallacy. The whole paper may be read with advantage to-day, and eighty years ago, when stethoscopy was in its infancy, the value of this article must have been great.

When Addison read before the Royal Medico-Chirurgical Society on February 28, 1854, his paper *On the Keloid of Alibert and on True Keloid*, he said that the last was "a disease, too, which, so far as I know, has not hitherto, with the exception of a slight allusion by Dr. Coley, been either noticed or described by any writer." In this statement he was wrong, for what he called "true keloid," which we now call scleroderma, had been previously described. Although priority cannot be given to Addison, his paper shows his power of observation, for he discovered the disease for himself.

In the *Guy's Hospital Reports*, 1839, Vol. IV. p. 1, is a short paper by him entitled "On the Disorders of the Brain connected with Diseases of the Kidneys." He describes the various cerebral symptoms which are found in cases of suppression of urine, retention of urine and renal disease, and says that if they are studied carefully, it is possible to feel pretty sure from their character that they are due to these causes. Further, he believes it is possible from such a study to form a good opinion as to which of the causes is operative in a particular case.

"On the Influence of Electricity as a Remedy in Certain Convulsive and Spasmodic Diseases" was published in the *Guy's Hospital Reports*, 1837, Vol. II. p. 493. It is a short communication, relating the beneficial effect of taking sparks

from the spine or passing shocks through the pelvis in patients affected with hysteria or chorea.

Addison describes in the *Guy's Hospital Reports*, 1836, Vol. I. p. 41, the case of a woman who had an ovarian cyst. She fell down and in so doing ruptured the cyst; its fluid was poured into the peritoneal cavity, but the woman recovered completely.

Soon after his appointment to Guy's Addison helped John Morgan, surgeon to the hospital, with experiments on the action of poisons. The result was a little book by Morgan and Addison entitled, *An Essay on the Operation of Poisonous Agents upon the Living Body* (London, 1829). The authors were "led to the conclusion that all poisons, and perhaps, indeed, all agents influence the brain and general system, through an impression made upon the sentient extremities of the nerves, and not by absorption and direct application to the brain."

A CASE OF ADDISON'S DISEASE, ASSOCIATED WITH HYPERTHYROIDISM AND VITILIGO

By NORMAN BURGESS, M.B., and E. C. WARNER, B.Sc.

A. A., aged 33, a motor driver, was admitted to Guy's Hospital under Dr. Herbert French on August 24, 1925, complaining of weakness, loss of weight, and indigestion.

The patient was of Anglo-Jewish parentage, and there was a good record of health in the family. He had one healthy child aged two years.

His previous illnesses comprised measles when young, chronic nasal catarrh, furunculosis while in the army, and at the end of 1918 a severe attack of influenza. He dated his final illness from the time of his demobilisation in October 1919, when he noticed that he became more than usually hyperpnœic on exertion; this continued, but it was not until nearly four years later (1923) that he became troubled by irregular periods of nausea and giddiness associated with feelings of exhaustion, faintness and flatulence. These persisted until his death. During these attacks he felt faint and giddy on waking and on occasion had actually reeled about, although he had never fallen; after breakfast this gradually passed off, only to recur the following morning. These periods were followed by periods of complete freedom from the attacks. During the two years prior to admission he had lost two stone in weight. He had also been troubled by a sensation of " pins and needles " in the fingers and toes, and especially of a general hyperæsthesia of the skin, which sometimes made his clothes unbearable. More recently he had complained of excessive salivation.

The skin condition needs special mention. In 1915 he first noticed a dark area of pigmentation on the left side of the neck; it was not until 1923, however, that it was obvious that he was becoming generally pigmented, and since January 1925 this had rapidly deepened in colour, until on admission the colour of the skin was as shown in Fig. 1. In April 1924 the first patch of vitiligo became superimposed on the general dark pigmentation. This was situated on the left side of the neck just below the area at which the dark pigmentation had commenced.

Recently the areas of vitiligo had greatly increased in number. In February 1925 the first of numerous small black spots

occurred, these being of various sizes, none bigger than the head of a pin. They were composed apparently of dense localised deposits of the dark pigment, superimposed on the already pigmented skin. None of these ever occurred on the areas of vitiligo. In February 1925 the patient was admitted to St. Bartholomew's Hospital with exophthalmos, tachycardia, tremors of the hands and fingers and general nervousness. At this time the basal metabolic rate was 32 per cent. above the normal.

Condition on Admission.—The patient was evidently of

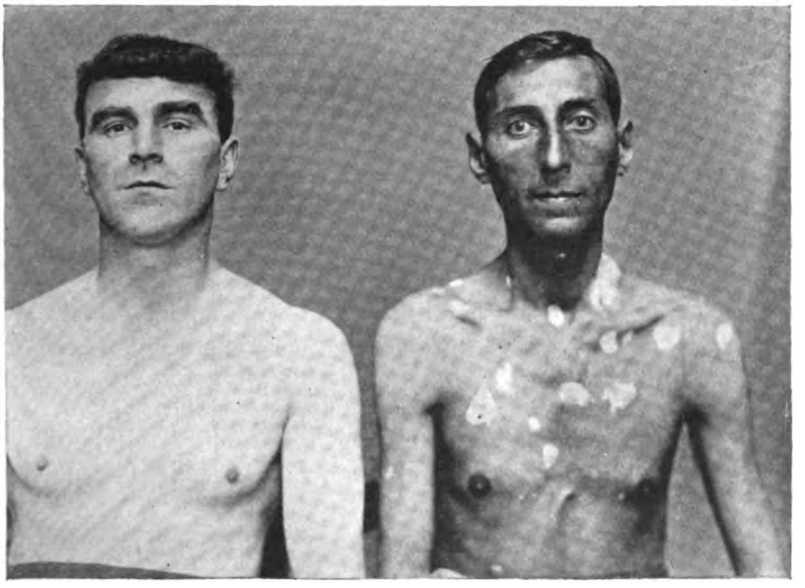


FIG. 1.

Case of Addison's disease with vitiligo and exophthalmos, photographed with a normal man to show degree of pigmentation.

nervous disposition; his movements were jerky and he was easily excited. The skin was deeply pigmented, the pigmentation being most marked over the lower abdomen and becoming less marked in the direction of the head and feet. The soles of the feet and the scalp were normal in colour, while the pigmentation was most marked in the areolæ of the nipples and the scrotum. Secondly, the lower part of the back was mottled, the light areas corresponding to the summits of hair papillæ, while the dark areas were the depressed areas between. Thirdly, there were small irregular deposits of black pigment, not larger than a pin's head and not raised from the surface. This same pigmentation was present on the palate, but not on the mucous

membrane of the cheek, and there was a small patch on the left sclerotic. Fourthly, there were extensive patches of vitiligo, most marked on the left side of the neck and trunk. Springing equally from the pigmented and leucodermic areas were fine, downy hairs.

The cranial nerves were normal, and the retinæ showed no abnormal pigmentation. The eyes were prominent and von Graefe's and Moebius' signs were present. The arm and leg tendon jerks were brisk; power and sensation were equal on the two sides; there was hyperæsthesia of the skin and the fingers showed fine tremors.

The respiratory and genito-urinary systems were normal. The heart was normal in position and size, and no abnormal sounds were audible. The spleen was just palpable.

Blood-pressure records were kept almost continuously. During the six weeks before treatment with adrenal extracts was begun the systolic blood pressure varied from 115 mm. to 85 mm., and the diastolic from 75 mm. to 45 mm. These compare with 103 to 109 mm. systolic and 65 mm. diastolic when in St. Bartholomew's in February 1925. Adrenalin was found to produce a greater rise of blood-pressure in the patient, than in normal persons.

The Wassermann reaction of the blood and the complement fixation against tubercle antigen were negative.

The following blood picture was obtained:

Red cells 3,760,000 per cub. mm.; hæmoglobin 69 per cent.; colour-index 0·92; white cells 6,050 per cub. mm.

Polymorphonuclear cells .	48 per cent.
Lymphocytes . .	38·5 ,,
Large hyaline . . .	9·7 ,,
Eosinophil . . .	2·5 ,,
Basophil . . .	0·5 ,,
Myelocytes . . .	0·75 ,,

There was no abnormality in shape, size or staining of the red cells, and none of them were hæmolysed by 0·48 per cent. NaCl solution. Further, the van der Bergh reaction applied to the blood serum was negative both by the direct and indirect methods.

The stomach, investigated by a fractional test-meal, showed complete achylia, and this was confirmed by estimation of the chloride content. The stomach emptied in 1¾ hours without regurgitation of bile. An x-ray examination of the alimentary tract showed a normal stomach with active peristalsis. In seven hours the stomach was empty, and the barium extended

from the cæcum to the splenic flexure. Traces were seen in the descending colon and rectum.

Cultivation of the stools showed no abnormal micro-organisms, nor were there any abnormal products of digestion or pigments in the fæces.

The lævulose tolerance test showed slight hepatic deficiency.

The urine contained a faint trace of albumen, but no other abnormal constituents, nor were there casts or abnormal pigments present. The blood area was 0·03 per cent.

An x-ray examination of the pituitary fossa did not show any abnormality in the sella turcica, nor was the pineal gland calcified.

The thyroid gland, which was rather difficult to feel, did not yield a thrill on auscultation. The basal metabolic rate was normal.

The thymus gland could not be percussed behind the sternum, nor located by the x-rays.

The suprarenals did not cast any shadows with the x-rays, which might indicate calcification.

An x-ray examination of the chest showed some perihilar fibrosis, but no evidence of active disease.

The muscular power of the hand grip was well below normal. Thus the left hand gave a grip of 45 units as against 90 units in the case of a patient with active phthisis, who was still pyrexial after two months in hospital. On the other hand, an ergographic tracing showed that the abductor indicis muscle did not tire any more easily than did the same muscle in normal controls. The electrical reactions of the muscles were perfectly normal and did not give any indication of a myasthenic reaction, though the glucose tolerance reaction to 50 grms. of glucose gave a result resembling that seen in cases of myasthenia gravis. The resting blood sugar was 0·097 per cent.; it rose to 0·245 per cent. in fifty minutes and had fallen to 0·088 per cent. in three hours. The urine after one hour contained a very minute trace of sugar.

The colour of the skin corresponded to a mixture of blue 3·0, red 5·0 and yellow 3·0 on the tintometer standard scale.

The patient could not be made to sweat by means of the hot-air bath alone, so pilocarpine nitrate gr. $\frac{1}{8}$ was given subcutaneously in addition. The skin sweated uniformly, the patches of vitiligo sweating as much as the pigmented areas.

The effect of a strong counter-irritant (mustard plaster) applied to a vitiliginous area of the skin was tried, as it was thought that possibly the vaso-dilatation might produce a re-distribution of pigment. To our surprise the white area was

unaffected, but the surrounding area of pigmented skin, on to which the plaster had overlapped, later peeled off, leaving white skin underneath. This soon became replaced by a fresh layer of pigmented skin, showing that the pigment resided only in the superficial layers.

Treatment and Progress.—The patient remained well, with an average blood pressure of 100 mm. (systolic) until October 2, 1925. During this time the skin became somewhat lighter and the spleen could not be felt. He was having dried thyroid gr. ½ twice daily, and dilute hydrochloric acid was given thrice daily with meals. On October 2, he began to be much more nervous, the tremors of the hands increased and the pulse-rate increased. He also began to suffer from nausea and diarrhœa. The thyroid was discontinued, but the diarrhœa and nausea with occasional vomiting continued for a week; the systolic blood pressure on October 10 was 93 mm.

On October 19 the oral administration of adrenalin solution (1 : 1000) was begun, ℥xxx being given thrice daily; this was increased on October 23 to six times daily. The blood pressure remained below 100 mm. during this time. As the patient again began to suffer from diarrhœa, the administration of adrenal was stopped on November 6, and the diarrhœa ceased. Suprarenal cortex, gr. ¼, was now given twice daily by the mouth. This did not raise the blood pressure. Nausea, dyspnœa and prurigo were complained of on November 13. The blood pressure was then 99 mm. The patient was kept in bed, and adrenalin (1 : 1000) ℥xxx was given six times daily by the mouth instead of the suprarenal cortex. The blood pressure from November 16 until November 24 averaged 118 mm. and was never below 105 mm. The patient felt better. Two teeth were extracted on November 25. The blood pressure fell to 95 mm. after this, and only on one occasion rose above 100 mm. from November 25 until December 19. The patient complained of flatulence during this time, and the prurigo caused him much discomfort. Oral administration of adrenalin was discontinued on December 7 and on December 20 subcutaneous administration was begun, ℥x being given night and morning. The blood pressure immediately rose, and from December 20, 1925, until January 29, 1926, the average blood pressure was 112 mm., only on one occasion falling below 100 mm. The patient felt much better and began to gain weight. Some new patches of vitiligo appeared in the mid-line of the neck and over the left arm. On January 13 the adrenalin had been increased to ℥x thrice daily.

On February 1 the blood pressure fell to 95 mm., and from that date the blood pressure only rose as high as 100 mm. on

three occasions. It was never below 83 mm. The fall in blood pressure was accompanied by nausea and fatigue on exertion. Flatulence and vomiting were also prominent symptoms.

On February 2 the adrenalin was increased to ℥xv thrice daily, and on February 12 to ℥xii six-hourly. A new pigmented spot had appeared on the palate. The administration of charcoal biscuits was begun on February 14, after which the patient felt better; the vomiting ceased, the flatulence diminished and his appetite returned. The blood pressure, however, did not rise above 95 mm.

The adrenalin injections were discontinued later in the month, as the patient began to fear them so much. From this time he gradually lost ground, becoming more and more feeble, with many periods of nausea and occasional vomiting, until he died in an exhausted state on March 19, 1926, his death being hastened by an attack of tonsillitis. Unfortunately a post-mortem examination was refused.

Discussion

The association of periods of nausea, giddiness, faintness and shortness of breath with a low blood pressure and pigmentation of the skin and palate makes the diagnosis of Addison's disease almost certain. Yet there are many anomalous features about the case. The duration of the symptoms since the first onset of fatigue (October 1919) is 6½ years, and if we reckon from the first onset of pigmentation (1915) is 11 years. It is very unusual for cases of Addison's disease to survive this length of time. Again, as far as we can find out, vitiligo is unknown in Addison's disease, although it is fairly common in Addison's anæmia and hyperthyroidism. Moreover, it seems clear that the patient was suffering from hyperthyroidism in February 1925, and to the end he still presented many signs of the disease, such as exophthalmos, Moebius' and von Graefe's signs, showing that it was not altogether quiescent even then, but could be stirred into activity by as small an amount of dried thyroid as gr. ½ twice daily.

The relationship of the hyperthyroidism to the Addison's disease is not certain, but it seems probable in this case, in view of the history, that the hyperthyroidism was secondary—and possibly compensatory—to the Addison's disease. This view is supported by the fact that his basal metabolic rate was normal in August 1925 compared with +32 per cent. in February 1925.

The absence of hydrochloric acid from the gastric secretion is of interest, because achlorhydria is recorded by Cabot in a

case of Addison's disease, in which the suprarenal glands were found at the autopsy to be tuberculosis.[1]

The normal blood sugar with a rather high rise after the ingestion of dextrose is contrary to the findings of some other observers.[2]

The observations on the sweating of the areas of vitiligo under the influence of pilocarpine are of interest in view of the work of Barber and Pembrey.[3]

We are indebted to Dr. Herbert French for permission to publish this case, and to the authorities of St. Bartholomew's Hospital for permission to quote their report on the case.

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THE ACHLORHYDRIA OF THE ADDISON'S (PERNICIOUS) ANÆMIA-SUBACUTE COMBINED DEGENERATION OF THE CORD-HUNTERIAN GLOSSITIS SYNDROME

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

In previous papers [1] I have given reasons for believing that the achlorhydria which is constantly present in Addison's (so-called "pernicious") anæmia and subacute combined degeneration of the cord is an essential predisposing cause of the disease and is not a result of the disease. I have also shown that there is abundant evidence that the achlorhydria is in many cases a result of constitutional achylia gastrica, an inborn and often familial error of function, which results in complete suppression of the secretion of gastric juice in spite of the apparently normal structure of the mucous membrane. But achlorhydria due to other causes may equally well predispose to the development of this disease. I have seen two cases, and Roth [2] has observed another, in which Addison's anæmia was associated with achlorhydria, which was apparently the result of chronic alcoholic gastritis, as cirrhosis of the liver was present. Typical Addison's anæmia has also been observed in patients with cancer of the stomach, in which no secondary deposits in the bone marrow were found after death. In the four cases recorded by Brandes [3] and in the only one of the kind I have seen complete achlorhydria was present. In the *Reports* for 1923 R. L. Waterfield [4] described a case under my care of subacute combined degeneration of the cord with Addison's anæmia in a man of 52, in which the achlorhydria was secondary to cancer of the stomach, and a similar case has been recorded by Garvey and Stern.[5]

The complete achylia which results from gastrectomy performed for cancer of the stomach may be followed by the development of Addison's anæmia (Hartman,[6] Moynihan [7]), and Ellis [8] has recently described a case of subacute combined degeneration of the cord associated with Addison's anæmia, in which the first symptoms appeared seventeen years after the performance of gastrectomy.

Lastly, the achlorhydria, which often follows gastro-enterostomy owing to the neutralisation of the gastric contents

by the alkaline juices of the duodenum and the rapid drainage of the stomach, has in rare instances been the precursor of Addison's anæmia (Campbell and Conybeare [9]; Willcox [10]).

The present paper is an attempt to discover the relative frequency of constitutional achylia gastrica and secondary achlorhydria as the predisposing cause of Addison's anæmia and subacute combined degeneration of the cord.

The question is one of great practical importance, as it should be possible to restore the secretion of gastric juice in some, at any rate, of the cases of secondary achlorhydria by suitable treatment, and the normal secretion of acid would clearly be of far greater value than the permanent administration of large doses of hydrochloric acid in first overcoming and then preventing the recurrence of intestinal infection in patients with Addison's anæmia and the associated conditions. The case recorded by Dr. M. E. Shaw in the present number of the *Reports* (p. 294) is of great interest in this connection.

A series of thirty-seven consecutive cases of the "Addison's anæmia—subacute combined degeneration of the cord—Hunterian glossitis syndrome" seen in private practice since 1922 have been analysed. A family history of Addison's anæmia may be taken as almost conclusive evidence that the achlorhydria is due to constitutional achylia gastrica, as it is this and not any constitutional abnormality of the blood or bone marrow which is the inherited condition. Faber [11] of Copenhagen has for many years taught that achlorhydria is always secondary to gastritis. Though I am convinced that this is not true, yet a carefully taken history shows that in a number of cases, in which there is no family history of Addison's anæmia, digestive symptoms of a type known to result from achlorhydria or the anæmia or nervous symptoms themselves are found to date from what appears to have been an attack of acute gastritis. In these cases the achlorhydria may be presumed to be the result either of the original acute gastritis or of chronic gastritis to which it gave rise.

Of the thirty-seven cases, twenty-one first sought medical advice on account of symptoms caused by anæmia, thirteen on account of nervous symptoms, two on account of glossitis, and one because she was anxious about herself in view of the number of her relatives who had died of Addison's anæmia. Though some degree of anæmia was present in nearly all the cases, and some of the primarily anæmic cases had nervous symptoms, they are classified under the headings (1) Addison's Anæmia, (2) Subacute Combined Degeneration of the Spinal Cord, (3) Hunterian Glossitis, and (4) Latent, according to the nature of

the symptoms for which the patient first sought advice. All without exception had complete achlorhydria.

(*a*) Addison's Anæmia

(i) *Constitutional Achylia Gastrica.*—Of the twenty-one cases with primarily anæmic symptoms, six gave a family history of anæmia, which was certainly Addisonian in three instances and probably in all (Chart I). The most remarkable case was that of a woman with Addison's anæmia, whose parents were first cousins, her father's father and mother's father being brothers. Her father and her mother's sister had both died of Addison's anæmia; unless this is a coincidence, they must have inherited the predisposition from either the grandfather or grandmother

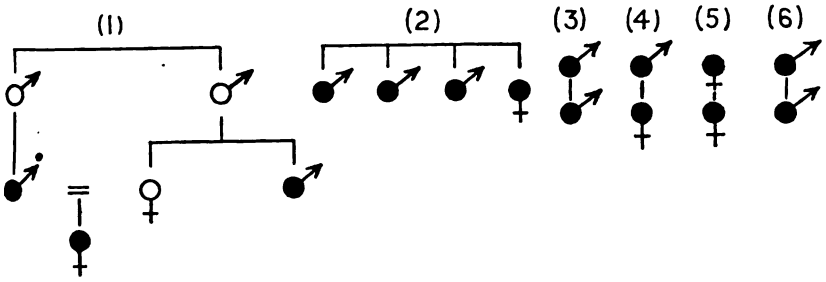

Chart I.

(Black circles indicate Addison's anæmia; clear circles no anæmia.)

they had in common. In that case our patient would be the fourth generation with a predisposition to Addison's anæmia, presumably in the form of achylia gastrica. Another patient, a man of 70, had two brothers and a sister who had died of the disease. In the remaining four cases the father or mother had died of anæmia. In none of these cases was any mucus present in the gastric contents, so that there was no evidence of gastritis.

(ii) *Post-gastritic Achlorhydria.*—One of the patients, a man of 62, had an attack of acute food-poisoning in Marseilles in 1914. The abdominal pain, vomiting and diarrhœa were followed by chronic diarrhœa, which was still present in 1922, when the first symptoms of Addison's anæmia developed. Some months later, when he came under our observation with severe anæmia and myocarditis, he was found to have complete achlorhydria. Directly he was given hydrochloric acid in large doses the diarrhœa stopped; it has never returned, but he still (April 1926) continues to take his acid, although he has also recovered from the anæmia and myocarditis. As no excess of mucus was present in the gastric contents, it is highly probable that the

achlorhydria was caused by permanent atrophic changes resulting from the acute gastritis in 1914.

Another patient, a man of 49, was poisoned by oysters in February 1923; he had severe vomiting and diarrhœa with abdominal pain, the digestive symptoms being followed by an attack of *B. coli* cystitis, for which he remained in bed for three weeks. His first symptoms of anæmia appeared in August 1925. When he came under our observation in March 1926 with severe and typical Addison's anæmia, he had complete achlorhydria, which persisted after preliminary lavage and was accompanied by excess of mucus in each fraction of the test-meal. In this case, therefore, the acute gastritis caused by the oyster-poisoning was presumably followed by chronic gastritis.

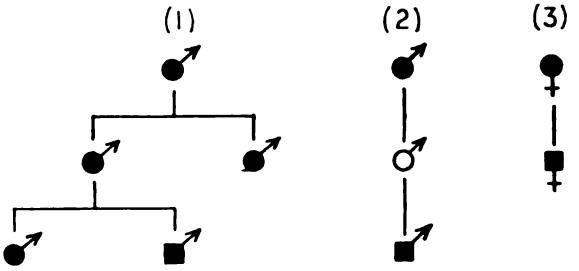

CHART II.

(Black circles indicate Addison's anæmia; black squares indicate subacute combined degeneration of the cord.)

(*b*) SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD

(i) *Constitutional Achylia Gastrica.*—Three of the thirteen cases of subacute combined degeneration of the spinal cord gave a family history of anæmia, which was certainly Addisonian in two instances and probably also in the third, the patient's mother having died of severe anæmia associated with a sore tongue (Chart II). The brother, father, paternal uncle and paternal grandfather of one, and the paternal grandfather of the other of the remaining cases died of Addison's anæmia. In two of these cases excess of mucus was found in the gastric contents. I have previously pointed out how liable individuals with constitutional achylia are to develop gastritis owing to the loss of the diluting, softening and antiseptic action of the gastric juice, so that the excess of mucus in these two cases can be regarded as evidence of secondary gastritis.

(ii) *Post-gastritic Achlorhydria.*—In three of these cases there was a history which suggested that the achlorhydria might be a sequel to acute gastritis. The first, a woman of 55, had accidentally swallowed some strychnine when seven years old,

and ever since had suffered from a "weak stomach." The second, a man of 54, gave a history of an attack of "ptomaine-poisoning" with severe diarrhœa in Switzerland: this was followed by six months of ill-health with indigestion, at the end of which the first symptoms of spinal cord degeneration appeared. The third patient, another man, had an attack of severe "gastritis" without obvious cause a year before his first nervous symptoms developed. The first two of these had excess of mucus in the gastric contents; the third had none. In each case the history suggests that the achlorhydria resulted from acute gastritis; in the first two the presence of mucus in the gastric contents showed that chronic gastritis was still present, so that recovery might possibly occur with a return of gastric secretion. In the last case, however, as there is no evidence of chronic gastritis, the achlorhydria is presumably due to permanent changes of an atrophic character.

(*c*) Hunterian Glossitis

(i) *Constitutional Achylia Gastrica.*—Neither of the two patients, who complained only of glossitis, though investigation showed that they had achlorhydria and megalocytosis, gave a history of Addison's anæmia.

(ii) *Post-gastritic Achlorhydria.*—One of the patients, a man of 57, dated his symptoms from a severe attack of diarrhœa two years before, which had followed the consumption of some very high pheasant. He had had a sore tongue on and off ever since.

(*d*) "Latent" Addison's Anæmia

The remaining patient, who was a woman of 50, and who was feeling quite well except for indigestion, occasional diarrhœa and eczema, sought medical advice mainly because she had become worried about herself owing to the number of relations on both sides of her family who had died of Addison's anæmia. Her sister, paternal grandmother and a cousin of her father's had died of it, a paternal cousin of her own has it now, and her mother died of it. Her tongue, which had been sore from time to time for three years, had the characteristic appearance of Hunterian glossitis; no filiform papillæ were present, the tip was red and the sides were scarred and bald. Her hæmoglobin percentage was 76, with 4,100,000 red corpuscles per cub. mm. (colour-index 0·92), and the average size of the red corpuscles was increased from the normal of 7·23 μ to 8·34 μ, but there was no anisocytosis and the red cells were perfectly normal in

appearance. She had complete achlorhydria, with slight excess of mucus, presumably due to secondary gastritis.

We can thus conclude that out of thirty-seven cases, ten, or 27·2 per cent., gave a family history of Addison's anæmia, so that their achlorhydria was almost certainly due to constitutional achylia gastrica. Six others, or 16·2 per cent., gave a history which strongly suggested that the achlorhydria was a sequel of acute gastritis and was not constitutional. In many of the remaining twenty-one the achlorhydria was probably due to constitutional achylia gastrica, as it is obvious that in only a proportion of such cases would more than one of the members of the family who had achylia develop Addison's anæmia or subacute combined degeneration of the cord. It is interesting to note that there was no overlapping between these two sets of

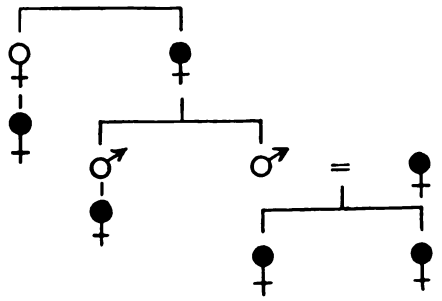

Chart III.

cases, none of those with a family history giving a history suggestive of acute gastritis, and none of the gastritis cases giving a family history of anæmia.

Addison's Anæmia and Subacute Combined Degeneration of the Cord in Relatives of Patients with Achlorhydria

In addition to the series of cases analysed above I have during the same period seen four patients, who consulted us for minor complaints and who were found to have achlorhydria, but no anæmia, spinal cord degeneration, or glossitis, and who gave a family history of Addison's anæmia. In these cases the achlorhydria, which predisposed to the development of anæmia or spinal degeneration in the relatives of my patients, must have been constitutional and not secondary to gastritis.

(1) The sister of a woman suffering from chronic diarrhœa, which was found to be due to achlorhydria, had died of Addison's anæmia.

(2) A woman with pyelitis, who had had no digestive symptoms and was only given a test-meal because she had told me that her sister had died of Addison's anæmia, was also found to have achlorhydria.

(3) A woman with neurasthenia but no anæmia was found to have achlorhydria. Two years later she wrote to say that her father had just died of " pernicious anæmia," and that her sister had been seriously ill for three years with severe anæmia, supposed not to be pernicious, though it was associated with achlorhydria.

(4) The brother of a doctor of 42, who consulted me for digestive symptoms associated with achlorhydria, had died at the age of 41 after being ill for eighteen months with subacute combined degeneration of the cord and terminal severe anæmia.

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A CASE OF APPARENT RECOVERY FROM ADDISON'S ANÆMIA AND THE ASSOCIATED ACHLORHYDRIA

By MAURICE E. SHAW, M.D., Medical Registrar, Guy's Hospital.

THE case about to be reported appears worthy of record on account of two unusual features. The patient has remained perfectly well with a hæmoglobin percentage within the normal limits for nearly three years, and the secretion of hydrochloric acid in his stomach has returned, although, on admission, he had the usual complete achlorhydria.

History of Case

The history of the case starts as far back as 1920. The patient is a man, now 37 years of age, a schoolmaster by profession. After serving in the 29th Division during the war, he was sent on military duty to Constantinople where, in 1920, the first symptoms appeared. In May of that year he began to lose his colour and became sallow in complexion. In July he suffered from repeated attacks of diarrhœa, associated with soreness of the mouth and tongue. Three months later he spent four weeks in hospital, apparently suspected as a case of dysentery, but no specific therapy was undertaken and there was never any blood in his stools. Improvement was only temporary, and he suffered from frequent recurrences of the diarrhœa and progressive pallor, the skin gradually assuming a typical lemon-yellow colour. In February 1921 he was invalided home to England and was sent to Millbank Hospital for a month. Some temporary improvement followed, but on the whole he got gradually worse during the succeeding six months. He had attacks of vomiting and began to lose strength and get short of breath. After treatment at Colchester Military Hospital he was re-admitted to Millbank under Major J. H. Spencer in October 1921. Major Spencer, who subsequently sent him to Dr. Hurst, kindly provided notes of the patient's condition and progress whilst under his care.

On admission to Millbank the patient's condition was " very serious : hæmoglobin below critical point (18–22 per cent.); red cells 740,000 per cub. mm.; marked poikilocytosis; mega-

loblasts present (scanty); white cells 4000 per cub. mm." A diagnosis of pernicious anæmia was considered probable in spite of the fact that at no time previous to his admission to Millbank had the colour-index been above one. The only alternative diagnosis considered was one of sprue, but " no positive evidence was obtained either chemically or clinically." Three transfusions were given at intervals of a month or more, a vaccine from the stools was prepared, and dimol and sodium cacodylate given. On February 28, 1922, after the third transfusion the blood count was : red cells 2,500,000 per cub. mm., hæmoglobin 52 per cent., white cells 3,500 per cub. mm., colour-index 1·04. A fortnight later he was discharged, but the hæmoglobin fell to 33 per cent. in June, and he was re-admitted for a further transfusion on the 9th of that month.

He was discharged from the army in February 1922, and took up work as a schoolmaster in March. Following the transfusion in June four further transfusions were given at varying intervals, but the records of the blood counts are not available. The lowest hæmoglobin percentage during these six months is known to have been 33 per cent. He was always liable to have reactions after transfusion, but this was considered to be due to protein sensitisation rather than to incompatibility. The blood was stated to be Group I.* The last transfusion of this period was on December 16, 1922, and it had to be discontinued after 300 c.c. had been given on account of severe rigors.

The general symptoms remained much the same during this period. He was very definitely yellow in colour and considerably troubled with shortness of breath. In addition he had lost several stones in weight. About this time he noticed from time to time transient numbness of the toes.

The patient first came under my own observation in January 1923, when he was admitted to Guy's Hospital under Dr. A. F. Hurst, whose house physician at that time I was. His colour was absolutely typical of Addison's anæmia. I saw him for the first time as he walked into the hospital, and I remarked to a colleague that he was an obvious case of Addison's anæmia and that he had no doubt come to consult Dr. Hurst. On going to the ward I found that both my surmises were correct.

He was actually admitted to Guy's (appropriately into Addison Ward) on January 4, 1923. Clinically the most striking

* When subsequently grouped at Guy's (see below) he was found to be Group IV (universal donor). It seems unlikely that the blood was wrongly grouped at Millbank, and possibly the numbering used there was the opposite of that commonly adopted in this country. On the other hand, if as a universal donor (IV) he was given the blood of a universal recipient (I), the reactions which were recorded would be abundantly accounted for.

feature was his colour, already alluded to, which faintly tinged the sclerotics. There was no other pigmentation of skin or mucous membranes, but the latter were extremely pale. He was thin without being markedly wasted. The tongue was clean and not sore, but had some deep longitudinal fissures and the filiform papillæ were completely absent. Some teeth had been extracted, and a few of the remaining ones were carious. There was no obvious pyorrhœa.

The pulse was distinctly water-hammer in type, but the heart was normal in size and no murmurs were present. It is not unusual to find a water-hammer type of pulse in patients with severe anæmias: it tends to disappear as the blood condition improves. The blood pressure was 100 mm. systolic, 60 mm. diastolic.

No abnormal signs were found in the lungs or nervous system. The urine was deeply pigmented, but was chemically and microscopically normal. It was not tested for excess of urobilin.

There was tenderness on pressure over both tibiæ and over the sternum.

The blood condition was as follows :—

Hæmoglobin . . .	42 per cent.
Red cells	1,670,000 per cub. mm.
Colour-index . . .	1·26
White cells . . .	6,718 per cub. mm.

Differential count :—

Polymorphonuclear cells .	46·22 per cent.
Lymphocytes . . .	50·42 per cent.
Eosinophils . . .	2·94 per cent.
Hyalines	0·42 per cent.
Basophils . . .	0 per cent.
Normoblast . . .	1 per cent.

Much poikilocytosis. Three corpuscles showed marked punctate basophilia.

The Price-Jones (cell diameter) curve was quite typical of the variety found only in Addison's anæmia (Fig. 1).

Van den Bergh's test for excess of bilirubin in the blood gave a positive indirect and negative direct reaction, which is characteristic of a hæmolytic anæmia.

A fractional test-meal showed complete achlorhydria.

The diagnosis of Addison's anæmia was therefore held to be established, and vigorous treatment was instituted on the lines laid down by Dr. Hurst. This treatment, it will be recalled, is

based upon the assumption that the toxins causing the disease are derived from an infection of the alimentary tract made possible by the absence of the gastric acid, which normally acts as an anti-bacterial barrier. To combat this infection a vaccine was prepared from a hæmolytic streptococcus isolated from the duodenal contents. After preliminary x-ray examination, which showed the presence of infection, all the remaining teeth were extracted. Hydrochloric acid was given in large doses (℥jss of the Ac. hydrochlor. dil. B.P.), as we had been able

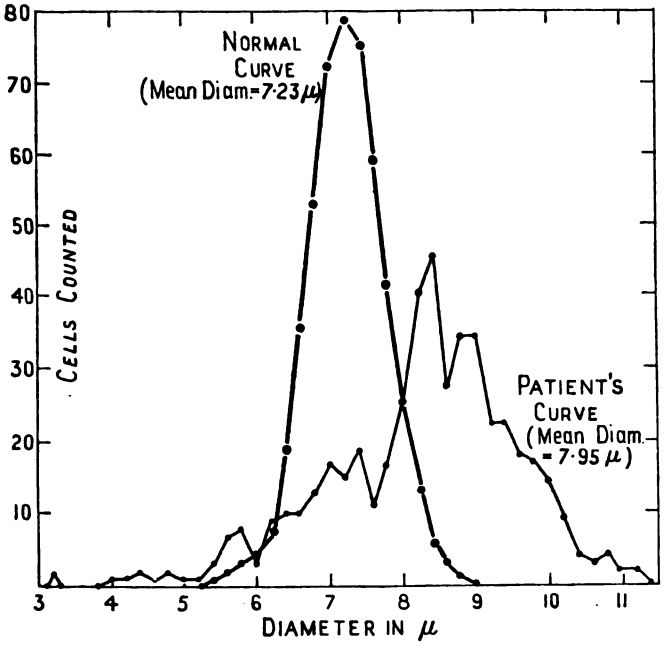

FIG. 1

Price-Jones cell distribution curve on January 8, 1923, showing megalocytosis, extreme anisocytosis, and irregular curve, typical of the active stage of Addison's anæmia. (J. W. Shackle and A. C. Hampson.)

to show that smaller doses produced little effect in raising the concentration of free acid in the gastric juice to a figure sufficient for disinfecting purposes. Half a pint of sour milk three times a day was also prescribed, and from time to time animal charcoal was administered with a view to relieving intestinal flatulence.

The remainder of the treatment was aimed at improving the blood condition. For this purpose there are only two satisfactory means available, arsenic and blood transfusion. A mixture containing Fowler's solution and iron and ammonium citrate was given throughout the patient's stay in hospital. On account of the severe reactions that had occurred after many

of the previous transfusions it was decided not to give a transfusion until the effects of the other therapeutic measures had been observed, or until the patient's condition rendered it absolutely necessary.

The blood condition got gradually worse during the three months following admission, but the fact that teeth were being extracted at intervals may have partially accounted for this. On March 21 the hæmoglobin had fallen to 30 per cent. and it was decided to transfuse. The recipient's blood was grouped and found to be Group IV. A Group IV donor was selected, and on March 27 (Hb. now 28 per cent.) a pint of citrated blood was transfused. He stood the transfusion well, better, in fact, than on any previous occasion, although the temperature rose the following day to 102·6°. On March 29 the temperature was down to normal, and the hæmoglobin percentage had risen to 47 per cent. He was discharged from hospital next day to recuperate in the country, and it was proposed, if progress was not satisfactory, to try the effects of splenectomy, as the spleen had recently become just palpable.

The records following his discharge from hospital are necessarily somewhat incomplete. Progress was slow at first: in fact the hæmoglobin percentage went down: on May 8 the blood was examined by Mr. J. W. Shackle, who reported as follows:—

Hæmoglobin . . .	25 per cent.
Red cells	872,000 per cub. mm.
Colour-index . . .	1·14
Leucocytes . . .	8,870 per cub. mm.

Differential count:—

Polymorphonuclear . .	58·1 per cent.
Lymphocytes . . .	34·2 per cent.
Eosinophils . . .	4·6 per cent.
Hyalines	2·9 per cent.
Basophils	·2 per cent.

Normoblasts infrequent (66 per cub. mm.) and all showed punctate basophilia.

In spite of the serious condition revealed by the above blood examination, the patient was feeling better than he had felt for some time, and apparently he was at the turning point of his downward progress. A hæmoglobin determination done later on, in the summer of 1923 (the exact date is not recorded), gave a figure of 75 per cent., and at this time the patient was looking and feeling remarkably well. In the autumn he was in robust health and had put on a great deal of weight; the hæmoglobin

was now 110 per cent. Two further estimations at about six-monthly intervals gave figures of 96 per cent. and 106 per cent. respectively, and on May 4, 1925, Mr. Shackle reported "Hb.

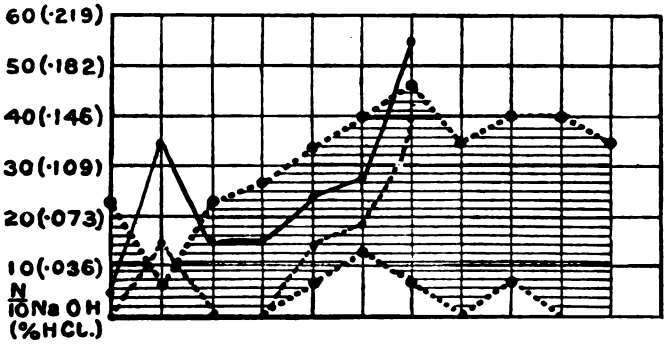

FIG. 2

Fractional hot meal in October, 1925. The shaded area represents the limits for free HCl (dimethyl indicator), of 80 per cent. of normal people.
..... represents free HCl, ———— represents total acidity.

107 per cent.: some pathological cells still present." Ever since the summer of 1923 the patient had been in perfectly normal health, except for recurrent attacks of indigestion, with which he had been troubled for years. He had been able to go

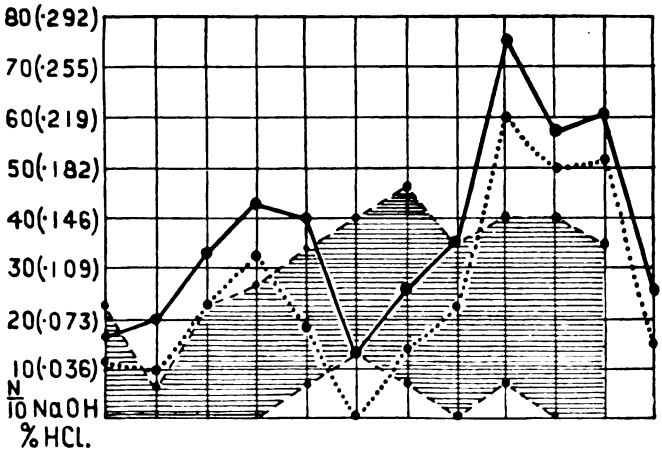

FIG. 3

Fractional test-meal in March, 1926.

back to his work as a schoolmaster and even to play Rugby football. He had been taking hydrochloric acid and sour milk ever since his discharge from hospital.

In October 1925 he was re-admitted to hospital under Dr. Hurst for a few days to have his gastro-intestinal symptoms

investigated, as these had been more troublesome recently. During the course of a routine examination it was discovered that free hydrochloric acid was now present in the gastric juice (Fig. 2). The hæmoglobin was 96 per cent.

On March 18, 1926, he was again admitted, this time with an attack of obstructive jaundice, which was unmistakably caused by gall-stones. No surgical treatment was undertaken and the condition cleared up completely in the course of a few days. A further test-meal was done and free acid was still

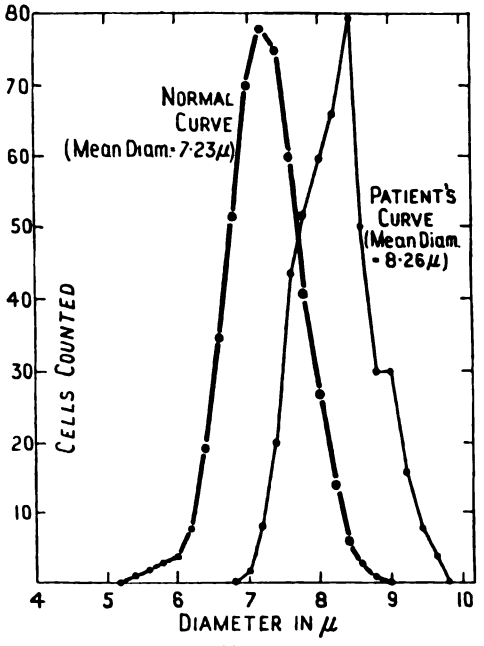

FIG. 4

Price-Jones cell distribution curve on March 15, 1926, showing megalocytosis, but no anisocytosis, and a very regular curve. (J. W. Shackle.)

found to be present (Fig. 3); in fact there was definite excess of acid two hours after the meal.

Mr. J. W. Shackle examined the blood at this time and found no abnormality in the film or the differential count. The hæmoglobin was 100 per cent., red cells 5,800,000 per cub. mm., colour-index 0·86, leucocytes 4,260 per cub. mm. The Price-Jones curve was markedly different from that done in January, 1923, but it showed that the mean diameter of the patient's cells had not become entirely normal (Fig. 4). The van den Bergh reaction, both direct and indirect, was completely negative, and had been so for at least two years.

The duodenal contents and bile (the latter obtained by administration of magnesium sulphate through the duodenal

tube) were examined by Dr. F. A. Knott, who reported the presence of *Bacillus coli communis* in moderate numbers both in direct film and on culture; no streptococci were detected.

The only additional point of interest in the history of the case is the fact that on two occasions since the blood condition returned to normal he has acted as donor for the transfusion of patients suffering from the same complaint. On neither occasion did any harm result, About a pint of blood was taken each time.

Discussion

It can, I think, hardly be questioned that the diagnosis of Addison's anæmia was correct in this case. The typical blood-picture, van den Bergh's reaction, lemon-yellow colour, achlorhydria, sore tongue and slight splenomegaly, with normal stools, are quite characteristic and definitely exclude sprue, as both the characteristic appearance of the tongue and the characteristic stools were never present. The important point is to determine whether we are dealing with a prolonged remission or with a definite recovery. The length of time that the patient has remained in perfect health with a normal hæmoglobin percentage (about three years) is certainly much longer than the average remission in a typical case of Addison's anæmia. Cabot's analysis of 524 cases quoted in Osler's Text Book gives a duration of three months to four years for the remissions. In the same investigation the figures for complete recovery are given as 6 out of 1200 cases. These figures are open to the objection that they were compiled at a time when the diagnosis of the disease was based almost exclusively upon the clinical features and the appearance of the blood film, and when the more recent diagnostic methods, upon which we mainly rely at the present time, were unknown. In a more recent investigation of 101 cases by Maitland Jones the average duration of the remissions is given as six months. It is clear, therefore, that the period of nearly three years during which the case here described has been perfectly well is a good deal longer than the remissions usually described. Have we any justification for arguing that we are here dealing with a case of recovery rather than with an abnormally long period of remission? An affirmative answer to this question appears to be justified by the remarkable fact that the gastric juice has regained its free acid. In the remissions commonly observed the achlorhydria persists in spite of the general improvement in the patient's condition. It is believed that the present case is the first in which a return of the gastric secretion to normal has been definitely demonstrated in a case of Addison's anæmia. Probably the more frequent use

of the test-meal in diagnosis will bring to light further cases. It is clear that the achlorhydria must be either a constitutional achylia or else secondary to an acquired gastric lesion. There is considerable evidence in support of the contention that in most cases of Addison's anæmia the achlorhydria precedes the onset of the symptom, whether the latter be due to disease of the blood or of the nervous system. No cases of this disease (including sub-acute combined degeneration of the cord) have been recorded in which the patient was known definitely to have had a normal gastric secretion at some previous date. There have, however, been several cases reported in which the disease followed an achlorhydria which may be presumed to have been acquired. The present case presumably belongs to this category, although it is not at all clear to what lesion the achlorhydria can be attributed. The most likely cause would appear to be an alcoholic gastritis, which is known to produce an achlorhydria and which cannot be considered an improbable lesion in an officer serving under war conditions in a semi-tropical climate. Such a lesion would naturally tend to disappear under the conditions of prolonged hospital treatment. It can certainly not be claimed that any therapeutic measure undertaken in his case can have had any effect in causing the change in the gastric secretion.

The progress of this particular case lends support to Dr. Hurst's contention that the achlorhydria is the primary lesion, which predisposes to the disease, and it appears likely that recovery has taken place *because* the gastric juice has now recovered its natural antiseptic properties. The treatment adopted has no doubt been of value in tiding the patient over the period in which his gastric juice was unable to act as an efficient anti-bacterial barrier. Now that the free acid has returned, the patient should remain well without further treatment, provided that he never again acquires achlorhydria. But even if the achlorhydria returned, it is quite possible that the patient has acquired sufficient immunity to deal with any intestinal infection which might result.

It is proposed to keep in touch with the patient whose history has been recorded, and any further information of interest will be reported in the *Guy's Hospital Reports*.

I am indebted to Dr. Hurst for permission to publish the records of this case, and to Mr. J. W. Shackle, who has been responsible throughout for the hæmatological work.

No references to the literature are given. A good bibliography will be found in Dr. Hurst's *Medical Essays and Addresses* (Heinemann), p. 107, 1924.

IMPRESSIONS OF RADIOGRAPHY IN AMERICA

By J. J. CONYBEARE, M.D., Assistant Physician to Guy's Hospital.

MOST hospitals in America are in a definitely stronger financial position than the voluntary hospitals in England, and this is reflected in the organisation and equipment of their x-ray departments. To a certain extent also the average American is more highly educated in regard to matters pertaining to his health, and in consequence there is a popular demand for x-ray examination, even in cases where actually there is little need for such an investigation.

The apparatus is modern and is provided on a very much more lavish scale than in England. Separate x-ray plants are provided for the taking of plates, which is always done by a skilled technician rather than by the radiographer himself. Control of the department is centralised in the hands of the senior " roentgenologist," who may hold either a part-time or full-time post. There are no artificial divisions into medical or surgical radiography, though in some clinics separate plants may be installed apart from the main x-ray department for the examination of special patients, such as those with genito-urinary disease. A small x-ray machine is usually also provided in the out-patient department, mainly for fluoroscopic work and teaching.

One point which is bound to strike the English visitor is the close co-operation between the x-ray staff and the clinicians. For example, at the Johns Hopkins Hospital the senior " roentgenologist," Dr. Baetjer, takes part in two conferences weekly, one with the professor of medicine and his associates, and one with the staff of the tuberculosis dispensary. At these x-ray conferences he discusses the radiograms of interesting clinical cases immediately following a discussion of the case from a clinical standpoint. Dr. Baetjer also attends the clinical pathological conferences conducted by the professors of medicine and pathology, and demonstrates the x-ray findings to the third and fourth year students. During working hours one of the " roentgenologists " is always to be found on duty in the x-ray department, and is always ready to give members of the clinical staff the benefit of his opinion. All the routine work of taking plates is in the hands of trained technicians, the results of whose work are eminently satisfactory.

This close co-operation between the medical and radiological staff is not a special feature of the Johns Hopkins. In practically all the hospitals I visited I found the radiologists anxious to correlate their findings with the clinical and pathological side of their cases.

All American hospitals have accommodation for a considerable number of paying patients in private rooms or small wards; where x-ray examination is required in these cases it is carried out in the hospital x-ray department at adequate fees. In some hospitals private patients may be sent by outside practitioners for x-ray examinations. The fees from paying cases are in most cases sufficient to defray the expenses of the department, including salaries for the "roentgenologists." In many cases there is a considerable surplus, which is handed over to the general hospital funds.

In addition to diagnostic work the x-ray department includes arrangements for treatment such as deep x-ray therapy. This is all centralised in the same building as the rest of the x-ray work and comes under the same administration and control. This is usually true of the dental radiography, which is also even more popular in America than at home.

I found opinion in America overwhelmingly in favour of the Coolidge tube as against gas tubes. Though it was admitted that excellent results can be obtained with the latter, in six months I never saw one in use. The great advantages of the Coolidge tube, according to the radiologists with whom I discussed the subject, lies in the standardisation of exposure and the certainty of obtaining satisfactory plates.

In alimentary tract x-ray work there are two main schools of thought, those who rely mainly on the fluoroscopic appearances, and those who insist on the taking of a large number of plates, even if the fluoroscopic findings are apparently normal. Thus at the Mayo Clinic, Dr. Carman is content with negative fluoroscopic findings and perhaps one or two negative plates. At Toronto, on the other hand, every patient sent for x-ray examination of the stomach and duodenum, even if nothing abnormal is seen on the screen, has upwards of a dozen plates or films taken before the examination is pronounced to be negative. Of these two are full-sized radiograms featuring the whole of the stomach, while the remaining ten are small films of the pylorus and duodenum; the latter are taken at intervals of a few seconds. Dr. Dickson of Toronto told me that with this technique a large number of small ulcers are diagnosed which would otherwise be missed.

At the Mayo Clinic the alimentary tract cases are examined

very rapidly, somewhere in the neighbourhood of thirty cases being seen in the hour. After the fluoroscopic examination in the erect position carried out by Dr. Carman or his assistants, the patients pass into another room where films are taken by technicians. If either the films or the fluoroscopic findings are in any way suspicious, the patients undergo a second examination on the following day.

Considerable attention was being paid to methods of visualisation of the gall-bladder originated by Graham in St. Louis. The intravenous method of injecting the opaque salt had been practically given up by the end of 1924 owing to the severe reactions that occurred. Extremely successful results were, however, being obtained with the oral administration of tetra-iodophenolphthalein in enteric-coated pills. These seemed rarely to produce any unpleasant symptoms and give an excellent shadow outlining the gall-bladder, provided the cystic duct is not blocked. The technique is to administer the pills, the dosage being regulated by the body weight, at 6.0 p.m. in the evening. At 11.0 a.m. on the following day the patient is examined fasting and plates taken, using the Potter-Buchy diaphragm. The patient is then given a meal and further plates taken half an hour later. If stones are present, the opaque gall-bladder is seen to have a mottled appearance. With a normal gall-bladder the shadow is usually smaller after the meal owing to the emptying of the gall-bladder during digestion.

In chest work the two features which impressed me most were the stereoscopic plates in cases of phthisis, and the use of orthodiagraphy in heart disease. Practically every case where the heart was suspected of being enlarged is examined orthodiagraphically, and the x-ray findings used to check the results of clinical examination.

At the Trudeau Sanatorium nothing but stereoscopic plates are employed. These are taken on a machine with an automatic plate charger and an automatic tube drop, and the results are really marvellous. Every patient in the sanatorium has a routine examination immediately after admission and another three months later. In the x-ray interpretation room at the sanatorium there is a most ingenious stereoscope devised by Mr. Sampson, the director of the department, which allows three people to look at the films at the same time, and which is also so constructed that pairs of films can be rapidly interchanged by rotating two drums. This greatly facilitates the comparison of films taken at different dates. At the Trudeau Sanatorium the x-ray work has been so perfected that it has now become almost the primary factor in diagnosis.

At the Trudeau Sanatorium considerable attention is also paid to the x-ray diagnosis of intestinal tuberculosis. The meal consists of 4 oz. of barium sulphate with 16 oz. of milk, flavoured with cocoa and sugar and thickened with flour; the patient is examined with the x-rays at the end of six, seven, eight, and nine hours and again after twenty-four hours. The most significant findings in enteric tuberculosis are hypermotility localised or generalised, and filling defects, which are constant. Of 1036 cases examined, 713 were negative and 323 positive, judging by the x-ray evidence. When cases came to operation or autopsy the x-ray findings as regards intestinal lesions were confirmed in nearly all cases. Mr. Sampson is convinced that intestinal tuberculosis is far commoner in cases of phthisis than is usually imagined, as there are usually few symptoms until the disease has become far advanced.

Films are much more popular than plates, mainly owing to the ease with which they can be stored. All lecture theatres are equipped with ground-glass screens of large size for the demonstration of x-ray films. The latter play a part in practically every clinical lecture and demonstration.

As regards medical education in x-ray work, students attend a short course of lectures given by the radiologist, in which he deals with the general principles of x-ray interpretation. No attempt, however, is made to familiarise the student with the technical details of the x-ray plant, which are considered to be the province of trained technical assistants.

RENAL DWARFISM

A STUDY OF THE COURSE OF THE DISEASE FROM SEVENTEEN CASES

By HUGH BARBER, M.D., Physician, Derbyshire Royal Infirmary.

UNDER the heading of renal dwarfism, interstitial nephritis in children is described in several recent text-books. This association of infantilism or dwarfism with chronic renal disease was emphasised in 1911 by Morley Fletcher, Reginald Miller and Parsons, since which time a number of papers bearing on the subject have been published. Before this date there are a number of publications referring to interstitial nephritis in children, in which the want of development is referred to, but not calling attention to the fact that this may be so obvious that it is the feature for which advice is sought by the parents.

Since putting together the notes of ten cases in the *Quarterly Journal of Medicine* for April, 1921, seven more renal dwarfs have come under my observation. These cases, together with the subsequent histories of the three still alive in 1921, enable me to add a few notes on the clinical features and course of this disease, based on the records of seventeen cases in all. The view that infantilism is too narrow a term to apply to the majority of cases has been confirmed. The usual clinical picture is one of late rickets. Other observers, notably Donald Paterson, have recorded cases in which rickets was present in infancy. Under these circumstances there is probably some different, or additional, ætiological factor.

Eight post-mortem examinations have revealed small kidneys, with pure interstitial nephritis. The smaller arterioles in the kidneys have shown some thickening microscopically, but clinically the arterial system has not shown changes marked enough to help in diagnosis and in only one case was the blood pressure above the normal.

In a disease so uniformly fatal the ætiology should make the most important problem for investigation. All the cases have been of the hospital class, but many of them from good hygienic surroundings, with healthy brothers and sisters. It has been a disappointing feature of this series of cases, that no hints as to the causation of the condition have been forthcoming.

The Clinical Picture

All the children have been dwarfed; the height towards puberty usually being about ten inches less than the average for the particular age. As the late rickets features, when present, are such an obvious indication of disease, and the interstitial nephritis signs so insidious in the absence of bone changes, it is reasonable to describe the clinical picture firstly without, and secondly with, bone deformity.

(1) *Without Bone Deformity.*—Only three of the seventeen cases died without any obvious bone deformities: aged 14, 15, and 22 years respectively One of these was under observation for seven years with thirst and polyuria; his want of development amounted to infantilism, and post-mortem the kidneys showed the most extreme changes of any case observed. However, five other cases have been in attendance for want of development, and have returned subsequently on account of genu valgum. Two of these had been recognised as renal dwarfs with straight legs, and in the other three the condition had been overlooked; one of them at my own out-patient department, at a time when I was familiar with this disease.

The clinical picture before the late rickets stage is not very striking. Thirst, polyuria perhaps with nocturnal incontinence, and general want of development are the characteristic features, varying in degree. Sometimes the thirst is so pronounced that diabetes insipidus is simulated. Albuminuria has been present in every case which has been carefully investigated; but not always in every specimen examined. It is probable that some cases die in this stage unrecognised, as it may be a very insidious condition. Arterial changes are not recognisable clinically, and hæmomanometer readings are normal.

(2) *With Bone Deformity: the Late Rickets Stage.*—In fourteen cases some degree of genu valgum has been present. In thirteen cases a special journey to hospital was made on account of this development. As stated above, two were already recorded as renal dwarfs with straight legs, who had been more or less lost sight of; and three had made a few attendances some time before, when deformities would have been recorded, if present. The earliest age at which genu valgum has developed has been seven years and the latest seventeen years—the usual time being between eleven and fourteen years of age. It would appear that bone deformities are probable towards puberty, when the nephritis has been present any length of time; but some have had symptoms, for example thirst, for several years before their development, and others been considered in reasonably good

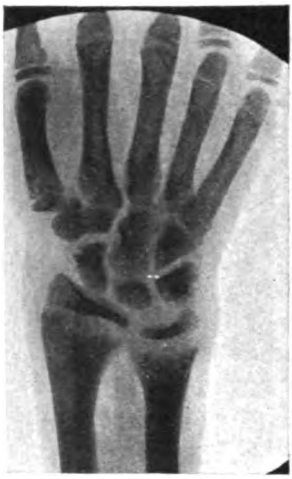

FIG. 1.
vy N. Renal Dwarf, aged 12½ years.

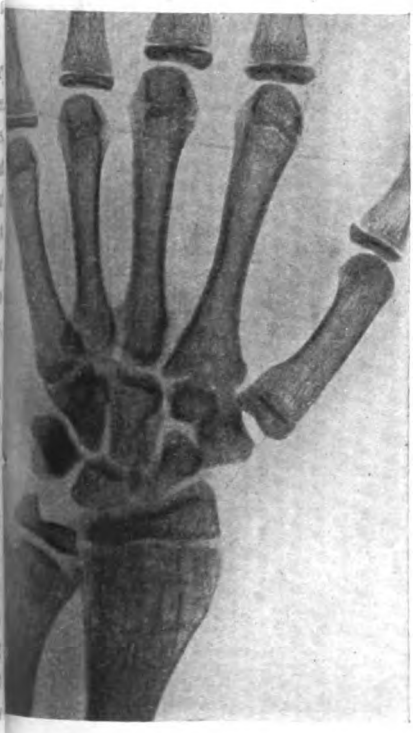

FIG. 2.
A case of Late Rickets, aged 15 years; of obscure ætiology.

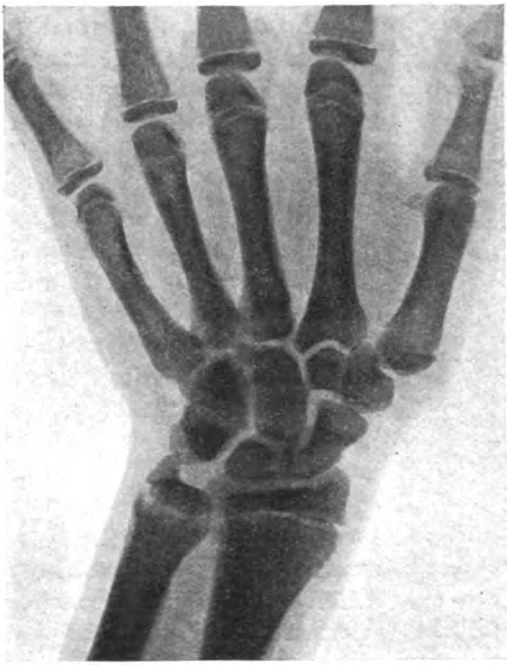

FIG. 3.
Ida F. Renal Dwarf, aged 16 years.

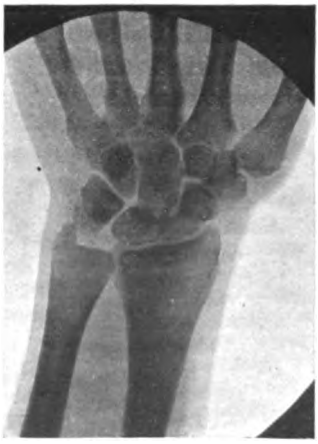

FIG. 4.
The same case, Ida F., aged 20 years, with ossification complete.

health, though small, until the knees became bent. The genu valgum develops comparatively quickly. The knees, wrists and ankles are the joints most obviously affected, but x-ray photographs will show changes in many others. Adolescent knock-knee is the most obvious clinical picture, but the wrists show the changes very clearly (Figs. 1–4).

A renal dwarf, with signs of late rickets, polyuria and albuminuria is quite characteristic. The want of development in some cases may amount to infantilism, just as it may in congenital heart disease and other conditions; but in most renal dwarfs, who have lived to an age when primary and secondary sexual characteristics should be developing, it will be found, that although these are rudimentary and delayed, they are present. Four of my cases have had menstrual periods: in one commencing in the fourteenth year, although genu valgum was marked and thirst had been present for ten years. Another case was admitted to the gynæcological ward, as an emergency for menorrhagia, when it was discovered that her case had already been published as a renal dwarf: in her case the interstitial nephritis has been confirmed post-mortem. It is somewhat surprising that her blood pressure was normal.

Diagnosis

Bilateral cystic disease of the kidneys and calculi in both kidneys may give rise to a urine similar to that of interstitial nephritis. Dr. Cameron mentions a case in which the latter condition caused renal dwarfism. In the absence of bone deformity, diabetes insipidus may be simulated. The diagnosis has been made comparatively easy by the introduction of the urea concentration test and the estimation of the urea in the blood. The urea test in eight different cases has given readings varying between 0·7 per cent. and 1 per cent. The blood urea in all these has been abnormally high, varying from 73 m.gm. per cent. up to 300 m.gm. per cent. These tests make the presence of albuminuria of less significance. In the sixteen cases, which have been carefully investigated, it was present in all, although quite exceptionally not found in one or two specimens, but present in the majority of specimens in every case.

By these tests the cases are distinguished easily from infantilism of obscure ætiology, thyroid dwarfs and cœliac disease. Looking more particularly for cases of bone deformity, one has seen four or five cases of late rickets, for which there was no apparent cause. These and other cases of adolescent knock-knee are clearly distinguished by the use of renal efficiency tests.

It would appear that x-ray pictures show more extreme changes at the epiphysial line in the renal dwarfs than in other cases of late rickets; but I do not think a diagnosis could be made on this alone (Figs. 1–4).

Prognosis and Course

The disease is fatal: uræmia usually developing in the second decade. But, as stated above, in the earlier years before the development of bone deformities interstitial nephritis might be overlooked. The age at death of fourteen cases has been, 11 years, 11 years, 14 years, 14 years, 15 years, 15 years, 16 years, 16 years, 16 years, 16 years, 17 years, 18 years, 22 years and 23 years.

There remain alive three cases:—

(1) Alice W., aged 19 years, height 4 ft. 6 ins., who had genu valgum six years ago. Three years ago the urea concentration test was 0·8 per cent. and the blood urea 146 m.gm. per cent. At the present time the urea test gives a similar reading; the blood urea being 164 m.gm. per cent. The blood pressure is 75 mm. diastolic and 120 mm. systolic. Menstrual periods have been regular for the past two years. The epiphyses are joined, but the bones less dense than normal. Her general health is fairly good, but she discarded the supports ordered for the legs and the genu valgum is marked.

(2) Ivy N., a recent case, aged 12½ years, with urea test 1 per cent. and blood urea 113 m.gm. per cent. Blood pressure 85 mm. diastolic and 100 mm. systolic. There is a long history of thirst. Genu valgum developed three years ago: the wrists show the changes well (Fig. 1).

(3) Ida F. (Case vii of the *Quart. Journ. Med.* series), whose case is exceptional in that she has had symptoms for seventeen years. She is now 20 years of age, height 4 ft. 5 ins., in fairly good general condition. The arteries are normal; blood pressure 75 mm. diastolic and 120 mm. systolic: the urea test is 0·7 per cent. and the blood urea 113 m.gm. per cent.: the urine of low specific gravity, with albumin small in amount. The knees are bent (she discarded the supports ordered seven years ago), but x-rays show that ossification is now complete (Fig. 4).

An outline of this last case will illustrate the whole course of this disease. She was an inmate of this institution aged 3 years, with thirst, polyuria and want of development, diagnosed as diabetes insipidus. The urine is recorded many times, always with low specific gravity, but albumin not detected. She contracted scarlet fever and was sent to an isolation hospital. She remained thirsty, with weak legs but otherwise well, surviving

an attack of measles. Genu valgum developed at 11½ years of age. She was sent up and admitted to a surgical ward for operation aged 13 years. Albumin was present in the urine. Sir Richard Luce asked me to see her, since when she has been under observation regularly. Menstrual periods began at 13½ years of age and have been fairly regular since. X-ray pictures showed typical changes but not very marked. Albumin was constantly present in the urine. Four years ago the urea test was 0·7 per cent. and the blood urea 73 m.gm. per cent. She has changed very little since then; looks fairly well and is mentally sound though uneducated. Ossification is complete, aged 20 years, and the legs might have been nearly straight if she had persevered with the supports.

This case and two others have lived to an age when the epiphyses have joined. The majority have died in the late rickets stage, towards the middle of the second decade. The onset of the interstitial nephritis symptoms is very insidious. There has usually been some degree of thirst, with want of development, obvious about 7 years of age; but one or two cases have appeared to be quite well, although small, until genu valgum developed towards puberty. One very striking case from the bone deformity point of view (Case iv *Quart. Journ. Med.*) was a notable footballer at school, although much undersized: his legs became crooked at 14½ years, for which he made his first visit to any doctor. Other joints were markedly affected. He died of uræmia aged 17 years, the interstitial nephritis being confirmed post-mortem.

It is not easy to foresee the length of time that is likely to elapse before uræmia develops. Three cases have lived several years with a urea test of less than 1 per cent. (after taking 15 grs. of urea). The blood urea is a better guide; figures of 200 or 300 m.gm. per cent. forecasting a short course. But one case (Alice W.) is alive and fairly well three years after a blood urea record of 146 m.gm. per cent.

Summary

This form of interstitial nephritis may be seen in three successive stages. In young children with want of development and thirst, usually an insidious condition, but sometimes simulating diabetes insipidus. Towards puberty bone deformities give the picture of a typical renal dwarf with late rickets signs. And later, the epiphyses may be joined. It is exceptional that this last stage should be reached. The course of the disease, in

one or two cases of this series, has been long enough to furnish records of all these stages.

In the first stage advice may not be sought, or the condition may not be diagnosed; which is the explanation why the late rickets picture has been the common one; many of the cases coming to the surgical departments, where I have been seeking them. There have been, however, three cases which have died without any late rickets changes, although the symptoms of interstitial nephritis were observed for several years.

The literature of late rickets is not very satisfactory; one reads of cases in which the joint condition was confirmed post-mortem; but no record is given of the cause of death. Of the two cases of adolescent knock-knee, which I compared in these *Reports* in 1922, one a typical renal dwarf, and the other late rickets of obscure ætiology, the former is dead and the latter alive and well. I think many, if not most, fatal cases of late rickets have been renal dwarfs.

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SOME OBSERVATIONS ON LIGHT-SENSITISATION *

By H. W. BARBER, M.B., Dermatologist to Guy's Hospital, and F. D. HOWITT, M.D., Chief Clinical Assistant to the Actinotherapeutic Department, Guy's Hospital, with some observations by F. A. KNOTT, M.D., Pathologist to New Lodge Clinic.

SOME years ago, one of us (H. W. B.) was consulted by a middle-aged lady, who for twenty years had suffered from an eczematous rash on uncovered parts, the exciting cause of the eruption being exposure to light. So sensitive, indeed, was she, that she was compelled to spend most of the spring and summer confined to the house, and even in winter she was never completely free from the eruption. This patient presented the signs and symptoms of profound intestinal toxæmia of the putrefactive type; she gave a long history of severe constipation, and her urine contained a large excess of indican. It was thought that possibly there was some connection between the light-sensitiveness and the intestinal toxæmia, and as the patient, who lived at a long distance from London, could not submit to any investigations, she was treated somewhat empirically by the internal administration of liquid paraffin, mild laxatives, full doses of hydrochloric acid after meals (the appearance of her tongue suggested hypochlorhydria) and a low protein dietary. The result was very striking, for within a few months her general health was greatly improved, the eruption disappeared, and she was able to go out in a boat on the open sea in summer without ill effects.

Later a similar case, but less severe, was met with, the patient being a man, in whom sensitiveness to light was of three years' duration. Details of this case are appended in the case summary at the end of this article (Case A). From this time further observations were made on similar cases of light-sensitisation, appearing for the first time in adult life, both in private and hospital practice, and comparisons were made with the juvenile type of the condition (hydroa vacciniforme, hydroa æstivale). In conjunction with Mr. J. H. Ryffel, to whose careful work and helpful advice we owe much, a series of patients belonging either to the juvenile or adult type were

* The greater part of this paper formed the subject of a thesis for the degree of M.D. (Camb.) submitted by one of us (F. D. H.) in June 1925.

investigated, chiefly with the object of determining the presence or absence of a porphyrin in the urine or fæces, which might be held responsible for the susceptibility of the skin to light. The results of these investigations will be dealt with later, but certain points may well be emphasised here:

(1) The number of cases of the *juvenile type* investigated was not sufficiently large to enable us to draw conclusions that might reasonably be applicable to all cases, but in three cases out of five examined *the fæces* contained a considerable amount of a porphyrin both *on a meat-containing and on a meat-free diet.* In two of them a porphyrin was demonstrable in *the urine* after it had stood for some time exposed to the air. The fifth case was investigated when no eruption was present.

(2) In no case of the *adult type*, of which a much larger number were investigated, was a porphyrin ever found in *the urine.* As regards *the fæces*, hæmatoporphyrin was often found, sometimes in considerable amounts on *a meat-containing diet*, and in two cases on *a meat-free diet.*

We were inclined to think at first that a porphyrin might be the sensitising agent in both types of cases, but that, whereas in the juvenile type it was found as the result of an inborn error of metabolism, and was independent of a meat-free or meat-containing diet, in the adult type its origin was, chiefly at any rate, the hæmoglobin contained in meat. The deficiency or total absence of hydrochloric acid in the gastric juice so frequently found in these adult cases might, we thought, have some connection with this formation of hæmatoporphyrin. This view was tentatively put forward by one of us (H. W. B.) [30] at a meeting of the Dermatological Section of the Royal Society of Medicine. But further investigations, made on normal controls and on other cases of light-sensitisation of the adult type, showed that hæmatoporphyrin was sometimes found in quite an appreciable amount in the fæces of the former, and that in the latter the quantity was not necessarily greater than in the controls. We therefore fell back on the conclusion that in the *juvenile type* the sensitising substance is probably often, if not invariably, a porphyrin, but that this is not so in *the adult type.* Further, as a result of the bacteriological examinations of the fæcal flora, of the frequent presence of indican in large excess in the urine, of the hypo- or a-chlorhydria so often found, and of the results of treatment in some cases, it was thought probable that the sensitising substance in the adult cases is a bacterial toxin, or possibly some product of abnormal bacterial action, absorbed from the intestinal tract.

A Short Resumé of Light-sensitive Diseases

The first suggestion that the action of light might be the cause of certain skin conditions was made by Bazin,[4] who, in 1855 and 1862, described the condition of hydroa vacciniforme. This he depicted as a vesicular or bullous eruption occurring on parts of the skin exposed to sunlight, appearing first in early childhood, recurring in summer and subsiding in winter. The lesions are usually vesicular, sometimes dark from hæmorrhage, becoming umbilicated and crusting, and finally leaving scars. The ears, alæ of the nose and fingers are occasionally destroyed. There is pain and itching.

In 1879 Hutchinson [16] described summer prurigo as a much milder and commoner condition than the above. It begins usually about puberty, recurs every summer, continues for many years, but finally disappears. The eruption consists of small red papules which do not pustulate; there is no ulceration or crusting, but small scars are left. It is slightly pruriginous. Hutchinson noted that rarely the disease begins in adults.

Fox [10] and Crocker [6] described similar cases, but in which vesicular or papulo—vesicular lesions occurred, and Adamson [1] took advantage of these to form a connecting link between the Bazin and the Hutchinson type. He also described the case of a girl who developed, at the age of seven, pin's-head, reddish-yellow papules, and a few vesicles on the face, arms and chest with itching. The condition recurred every summer, leaving scars. At eleven years of age, large vesicles occurred, becoming opaque and scabbing. On being removed from the sun, the lesions disappeared, but with further exposure on the balcony tense, clear bullæ, eventually crusting, broke out on the face and ears. Adamson concluded by suggesting that in summer eruptions there is probably a toxæmia producing skin lesions of an inflammatory but amicrobic origin determined by ultra-violet rays and possibly other agents. He drew attention to the fact that pellagra and lupus erythematosus are also influenced by sunlight.

The first definite suggestion as to a possible photo-sensitising agent in hydroa cases came from McCall Anderson [2] in 1898. He published the case of two brothers, aged respectively twenty-six and twenty-three, in each of whom an eruption appeared at the age of three on exposed parts, chiefly the nose. This recurred every year, in the summer, beginning with itching and the formation of blisters, which burst, became crusted, and were followed by cicatrisation, contraction, and eventually considerable deformity. The urine in each case was the colour

of light burgundy, and here the only difference in the two cases appeared, namely, that in the elder brother the urine was normal between the attacks, whereas in the younger the abnormal pigment was constantly present. On examination the urine was found to be acid and to contain no protein, bile-pigment or hæmoglobin. Spectroscopically, it was found to contain the four bands of alkaline hæmatoporphyrin, which, on the addition of strong H_2SO_4, was changed to the two-banded acid hæmatoporphyrin.

Hæmatoporphyrin in very minute traces can be demonstrated in normal urines. Günther [12] grouped definite porphyrinuria under four headings:

1. Acute toxic. (Sulphonal poisoning. Sobernheim [26] showed that after prolonged administration of sulphonal, hæmatoporphyrinuria appeared.)
2. Acute (not due to drugs).
3. Chronic.
4. Congenital.

Only in groups 3 and 4 is hydroa æstivale found. Günther, then, was the first to recognise the existence of an inborn error of metabolism in which the excretion of porphyrins in the urine is but one symptom, and he gave to it the name of Hæmatoporphyria Congenita. Garrod [11] reviewed all the cases, which then numbered nineteen, and contributed largely to the subject. He gave further information concerning the two brothers, described by McCall Anderson, who died respectively eight and nine years later. A sister appears to have had the same complaint and to have died at fifteen. Most of the cases collected by Garrod appear to have had hæmatoporphyrinuria at an early age, and to have succumbed early, but a patient of Nebelthau and Vollmer died at sixty-five and passed red urine all her life. In support of his contention that this condition may result from an inborn error of metabolism, Garrod was able to show a case which had passed red urine and fæces from birth. A bullous eruption had appeared on the face and hands at three months, and at nine months a pink tooth had been cut. On transillumination the bones were opaque also, due to deposition of porphyrin.

A considerable amount of work has been done with the object of discovering the origin of porphyrins in the body, but no definite conclusion has been reached. Fischer [9] suggested that they are formed as an intermediate product in the conversion of hæmoglobin into bilirubin. If this is so, it would appear that in the congenital cases there is an absence of some specific enzyme causing an arrest at the stage of porphyrin

formation. It would not then be necessary, as Garrod observes, to invoke any excessive hæmolysis to account for the excretion of porphyrins in the quantities observed. It is, however, of interest to note that excessive hæmolysis may cause hæmatoporphyrinuria, and Pal [21] has recorded a case of this associated with Raynaud's disease. But blood-counts in the cases under consideration show no evidence of such hæmolysis. Stokvis,[27] on the other hand, suggested that porphyrins might be formed in the alimentary tract from muscle pigment or even chlorophyll.

Ehrmann [8] studied cases of hydroa vacciniforme, and found porphyrins to be present during attacks in the urines, and Linser [18] considered that hæmatoporphyrin was liberated from blood-pigment by the action of ultra-violet rays. Hæmatoporphyrin is an artificial product, the porphyrins occurring in the body being uro- and stercoporphyrin, and Fischer showed that they had different formulæ. He is also of opinion that uroporphyrin predisposes to toxic symptoms, whilst stercoporphyrin predisposes to sensitisation of the tissues. Porphyrinogen is the colourless precursor of these substances, and does not show the spectrum of the porphyrins; therefore it is possible that porphyrinogen is present in the intervals between the attacks in these cases. Although Garrod believes many cases to be congenital, he says "there can be no doubt that porphyrinuria is, in some instances, a symptom of acquired disease, and that, if chronic, it may give rise to hydroa. We are not justified in supposing that porphyrins are the only photo-sensitising agents concerned in the causation of hydroa æstivale. They might, however, more commonly be found, particularly as in all cases so far described the urines, but not the fæces, have been examined."

There is one other condition due apparently to a photosensitising agent, and that is the disease known as Fagopyrismus, which occurs as the result of poisoning by buckwheat. Although primarily a disease of white, or white-spotted animals, chiefly swine and sheep, it has occurred in man (H. L. Smith [25]). The animals on exposure to the sun develop a severe dermatitis of the white parts only, the black remaining normal. If, however, the animals are kept away from the light, nothing whatever occurs. The sensitising agent at work here is, presumably, phyloporphyrin, a derivative of chlorophyll and a constituent of buckwheat. Chemically, this substance closely resembles hæmatoporphyrin.

There is evidence, too, that in pellagra a sensitisation may occur to some toxin in the food, possibly in this case a constituent of maize.

Experimental Work on Photo-sensitising Agents

The discovery of photo-dynamic action goes back to Raab [23] and Tappeiner,[28] who examined the action of acridin hydrochloride on paramœcium on exposing them to light. Von Pappeiner performed similar experiments with eosin and methylene blue, whilst Sachs and Sacharoff [24] used erythrocytes in solutions of photo-dynamic substances, and showed hæmolysis to take place in the light. Hausmann [13] injected white mice with hæmatoporphyrin and exposed them to sunlight and carbon arc lamps. With diffuse light a characteristic œdema was produced, and when the animals were again placed in the dark, thrombosis and necrosis occurred. With strong light a very violent prurigo appeared, the skin became much reddened and death took place. Sometimes death was immediate and some of the symptoms recalled those of protein poisoning, suggesting that a condition of sensitiveness may be maintained by the normal traces. Nothing whatever occurred if the mice were never exposed to light. Finally, Meyer-Betz [20] injected himself with hæmatoporphyrin, and exposed himself to different forms of light. With ordinary sunlight there was burning and prickling on exposed parts with reddening and swelling and pigmentation, the whole surface reacting equally and affecting only the epidermis—a picture resembling dermatitis solaris, a condition in which hæmatoporphyrinuria is unknown. With the Finsen lamp, however, hard, painful bullæ with hæmorrhages and scabs, leaving deep ulcers, were produced—a condition identical with hydroa vacciniforme.

A considerable amount of work has recently been done with the object of determining the exact rays in the solar spectrum responsible for the various effects produced by exposure to light. Impetus has been given to these investigations by the recent application of artificial light for therapeutic purposes. The problem has been attacked from many angles; for example, the determination of the alterations in the red and white cell-counts and in the bactericidal power of the blood before and after exposure. But here we are only concerned with two questions, namely, the penetrating power of the various rays, and the production of such phenomena as erythema, pigmentation, and the lesions in the diseases under discussion.

It now seems definitely established that it is the rays of long wave-length which have the greatest penetrating effect. According to the work of Burk, 20 per cent. of the red and yellow rays, and 1 per cent. of the blue and violet are allowed to pass through the skin. Freund found that skin of the

thickness of 1 mm. will only permit rays of wave-length greater than 3,600 Angström units to traverse it, and that 2·5 mm. are opaque for rays of over Å. 4,300.

Hausser and Vahle [14] exposed small areas of the skin of the arm to isolated ultra-violet rays by means of a large quartz spectroscope. They observed that ultra-violet rays of about Å. 3,130–2,530 produced an erythema, the maximum being achieved with Å. 2,970. They admitted that rays above and below these figures are also capable of producing slight erythema. Johansen [17] considered that 72 per cent. of light erythema is caused by rays of Å. 3,020–2,970.

Dorno [7] measured the intensity of heat and ultra-violet radiations at Davos at different periods of the year, and O. Bernhard [5] noted the relative erythema and pigmentation produced at these times. They concluded that pigmentation is prevalent at the time of greatest relative heat intensity.

Many attempts to reproduce the lesions in cases of hydroa æstivale have been made, but usually without success. Martenstein [19] claims to have achieved this using all ultra-violet radiations.

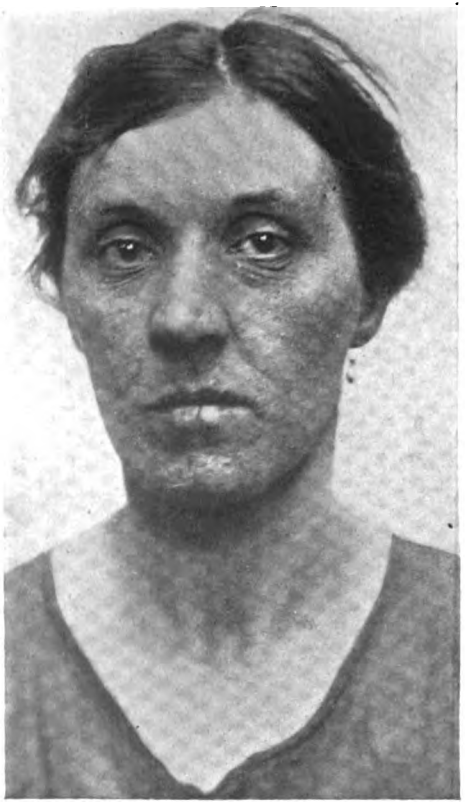
Leonard Hill [15] performed some interesting experiments to test the effects of different light rays upon the frog's mesentery immersed in a saline bath. Using the mercury-vapour and carbon-arc lamps he found that stasis was produced in the vessels, whilst no stasis was produced when the ultra-violet rays were excluded by the intervention of a quinine filter. He now added a solution of hæmatoporphyrin to the saline, and found that stasis occurred in the presence of visible rays alone, together with the production of thrombi. He concluded from this that ultra-violet rays alone are capable of producing stasis, whereas visible rays also produce it, together with thrombosis, in the presence of hæmatoporphyrin. He also found that melanin in fine suspension completely destroyed the action of ultra-violet rays.

Clinical Observations

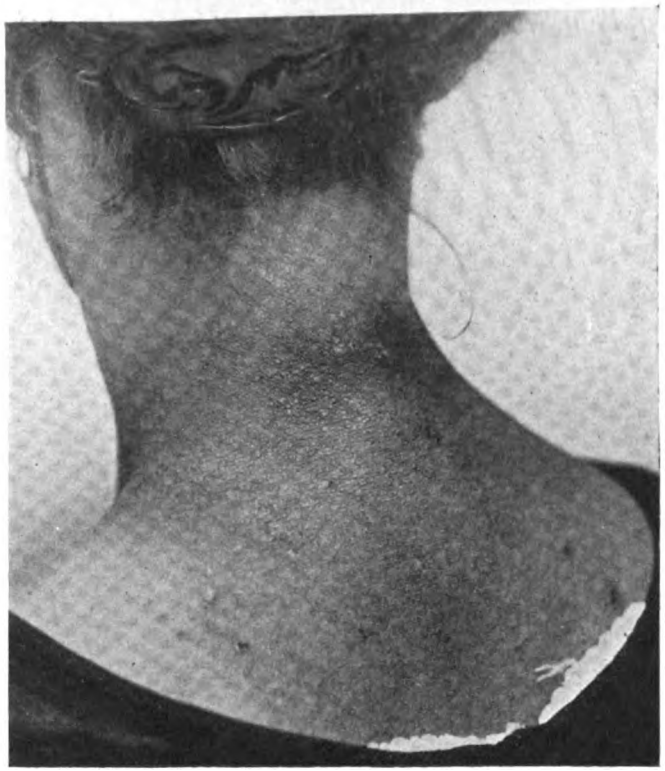
The following observations have been compiled from cases presenting themselves for treatment at Guy's Hospital Out-patient Department during the last three years.

From these investigations it appears that all cases of light-sensitisation may be divided into two groups, which will be referred to respectively as the adult and juvenile types.

The clinical features of what may be called the adult type of light-sensitiveness are so characteristic that the condition may be diagnosed at a glance. Females are affected far more



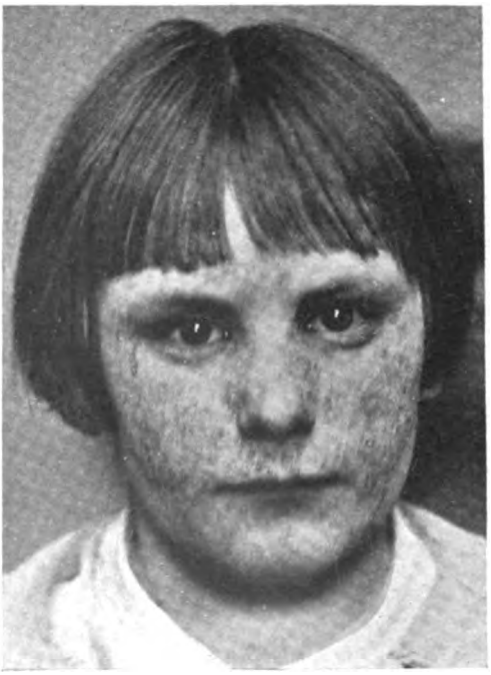
The skin is harsh and much thickened, especially around the lips and chin. The natural lines are accentuated.



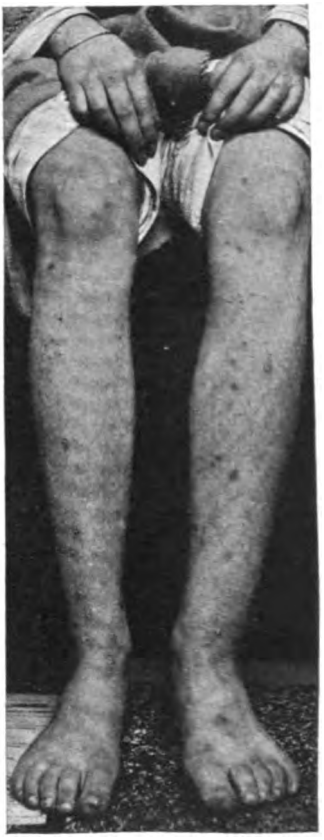
Note lichenified papules, the result of chronic irritation.

Case 11. *Adult* type of long standing.

commonly than males, the converse being true in the juvenile type—*hydroa vacciniforme seu æstivale.* The patient's complexion, even when no active eruption is present, has a sallow, earthy tint, and the vermilion border of the lips is of a characteristic bluish-grey colour. In cases of long standing the skin



The forehead, protected by "fringe" of hair has escaped.



Same case after exposure for one afternoon on balcony. Note crust formation of bullæ, into some of which hæmorrhage has taken place.

Case 16. *Juvenile* type.

of the face, neck and other exposed parts is definitely thickened, and the natural lines are accentuated, the changes being doubtless partly due, as in ordinary lichenification, to the incessant rubbing and scratching which the intense irritation provokes. The appearances are, in fact, very similar to those seen in the generalised prurigo that is so common in patients with the asthma–hay-fever–urticaria–eczema–prurigo complex.

The actual eruption which appears on uncovered parts, when the patient is exposed to light of a certain intensity, is in the early stage an erythema, with a varying degree of serous exudation, the affected areas of skin being bright red and somewhat œdematous. Eczematisation, which is always an indication of epidermal sensitisation, then supervenes, and in an acute attack, numerous, close-set eczematous papules and

Case 13. *Juvenile* type.

vesicles arise on the preceding erythematous base. The eyelids are often swollen, as in an eczematous dermatitis produced by chemical or other irritants.

These acute outbreaks are seen most commonly in early spring, and occasionally, after their subsidence, the patients may suffer little inconvenience throughout the summer, except on exposure to strong sunlight. More commonly, however, a chronic eczematisation of the face, neck and the backs of the hands and wrists succeeds the acute phase of the eruption, and the patient experiences paroxysms of intense irritation, which

may seriously interfere with sleep. On the nose, malar regions and chin, serous exudation from the eczematous vesicles constantly takes place, drying up to form yellowish crusts. The skin becomes harsh and thickened from the chronic inflammation, and gradually lichenification results owing to constant rubbing and scratching. On the neck and backs of the hands, discrete lichenified papules, similar to those seen in the juvenile cases, are often present.

It will be observed that the clinical features of the eruption in these adult cases differ materially from those that characterise the juvenile form of light-sensitisation. In the latter the lesions consist of discrete papules, papulo-vesicles and bullæ, which dry up to form crusts, and frequently leave pitted scars. In the former the cutaneous reaction is more superficial and of an eczematous nature, and even in the most severe cases scarring, apart from secondary pyogenic infection, is never seen. It would seem that the early inflammatory changes in hydroa vacciniforme are primarily dermic, whereas in the adult form the reaction is, as has been said, more superficial, and due to epidermal sensitisation.

Investigations

The urine.—Protein, blood and sugar were absent in all the urines examined. Indican was found in most of the adult cases, never in the juvenile type. Every urine was tested for hæmatoporphyrin by adding acetic acid and extracting with amyl alcohol. It was found in two of the more severe cases of the juvenile type (Nos. 12 and 14) after the urine had been allowed to stand for a few days on exposure to the air, but was absent when the urine was examined fresh. Possibly this was due to the conversion of porphyrinogen, already present, to hæmatoporphyrin; but the addition of potassium permanganate in order to oxidise any porphyrinogen present, as suggested by Perutz,[22] did not give the spectrum of hæmatoporphyrin. Nothing abnormal could be detected with the spectroscope in urines of the adult type.

The fæces.—The consistency and chemical constitution of the fæces were, as a rule, normal. In the fæces of the juvenile type, porphyrins were present both on a meat-containing and on a meat-free diet. The guaiac test was negative. In the adult cases the results were inconclusive. On a full diet the guaiac test was positive and hæmatoporphyrin usually present. When meat and green vegetables were excluded from the diet, the guaiac test became negative, and this was as a rule followed by the disappearance of

hæmatoporphyrin. In one or two instances, hæmatoporphyrin remained in the fæces. This persistence after the stools have become negative to guaiac, however, sometimes occurs in normal subjects, and is due, presumably, to one of two causes: (*a*) A small portion of the food may be held up somewhere in the intestines, and passed several days later. (*b*) There may be some slight ulceration high up in the alimentary canal, insufficient to cause symptoms or to produce a positive guaiac test. The fæces of the adult type, may, therefore, be taken as normal in this respect.

On bacteriological examination no unusual organisms were found in the juvenile type. In the adult cases the total number of proteolytic anærobes appeared to be relatively high, and in addition to the customary ærobic fæcal flora, numerous colonies of such organisms as yellow staphylococci, long-chained streptococci or unusual coliform bacilli were grown. The offending organism was not constant, but among the ærobic organisms a long-chained streptococcus or a coliform bacillus of the Friedländer type was most commonly found. As a rule there was no definite colitis, but this was present in two cases (Nos. 17 and 19).

In order to prove whether hæmatoporphyrin is formed in the alimentary canal, by the action of various bacteria on blood, the following technique was employed by Dr. F. A. Knott.

A fæcal specimen from each of six cases (two juvenile and four adult) was cultivated aërobically and anaërobically. The aërobes were isolated as pure cultures of each strain present. The anaërobes were grown as a mixed culture and isolation of individual strains was not attempted.

From each aërobe and each anaërobic mixture a subculture was made into—

1. A sterile tube containing 10 c.cm. of nutrient broth and 0·5 c.cm. of whole normal blood.

2. A sterile tube containing 10 c.cm. of nutrient broth and 1 c.cm. of laked blood (by addition to the blood of sterile distilled water).

These subcultures were incubated continuously at 37° C. aërobically, or anaërobically, as necessary, for several days.

Each day the tubes were examined spectroscopically for the absorption bands of hæmatoporphyrin. The test was first applied to the upper layers of the broth, that is, those above the bacterial growth, and the tubes were then shaken up, and the whole contents examined with the spectroscope.

The tests were continued up to the fifth day. In none of the tubes did hæmatoporphyrin bands at any time appear.

Dr. F. A. Knott has kindly prepared sterile fæcal extracts from four of the more severe adult cases of light-sensitiveness in which abnormal bacteria have been grown. The extracts were prepared by suction through a very fine porcelain filter and their sterility proved. The backs of rabbits were carefully shaved and all local irritation from the shaving allowed to subside. Injections of the sterile fæcal extract were then made intravenously on the ears of rabbits, and the animals, together with a shaved control, were placed in the sun.

The exposed skin of one rabbit so injected (from Case 3) became markedly erythematous; there was considerable exudation, which crusted, and the skin bled when the crusts were removed. The control rabbit, not so injected, showed no reaction on the same exposure. Another animal (from Case 11) gave a similar but less marked reaction. With the other two (Cases 1 and 5) the results were negative. Much more work will have to be done, however, using fæcal extracts from normal subjects as controls, before this point can be established.

Test-meals.—A fractional test-meal was performed on all these cases. A pint of porridge was given on an empty stomach, and samples of the gastric contents drawn off every quarter of an hour by means of Ryle's tube, and examined for free and combined hydrochloric acid. Titrations were made against decinormal NaOH, using Töpfer's reagent for free, and phenolphthalein for total acidity.

The gastric secretion in the juvenile cases was always normal. In all the adult cases except two, a marked hypochlorhydria, sometimes amounting to an apparent complete achylia, was found. In the two exceptions, one showed a normal curve, the other had an actual hyperchlorhydria.

X-ray examinations.—A barium meal was given, and its passage through the stomach and duodenum observed. The patient was screened at intervals of six, twenty-four and forty-eight hours, and the progress of the barium through the alimentary canal observed. In the juvenile cases food passed normally through the whole tract. In the adult cases stasis was nearly always found. A certain degree of visceroptosis and kinking appeared to be responsible in some, in others the delay appeared to be due to sluggish peristalsis in the large intestine.

The blood and serum.—The red cell-counts were normal in all the cases of light-sensitisation observed.

The serum was examined for hæmatoporphyrin, but this was never found.

With the object of attempting to prove whether any abnormal

destruction of red cells occurs in these cases as the result of the action of light, the following experiment, suggested by Dr. Cranston Low [33] and carried out for him by Dr. Hedley Wright, was performed upon two juvenile cases, two adults and two normals as controls:

About 10 c.cm. of blood were withdrawn in the ordinary way and centrifugalised, the serum being pipetted off. Another 2 or 3 c.cm. were withdrawn into a sterile test-tube containing calcium citrate solution to prevent clotting, and from this a preparation of washed red cells was made by repeated addition of normal saline and pipetting off the supernatant fluid. Both preparations were kept in an ice-chest to prevent hæmolysis by bacterial agency: 1 c.cm. of serum was then taken, and to this was added 0·2 c.cm. of washed red cells, and 0·8 c.cm. of normal saline. The mixture was then placed in a quartz test-tube, and exposed to the light of a mercury-vapour lamp for one hour at a distance of one foot.

No hæmolysis was observed in any case, though slight "pinking" subsequently took place in one of the "normal" and one of the adult tubes, probably due to bacterial infection. No hæmatoporphyrin was liberated in any case.

Prognosis and Treatment

The prognosis and treatment differ substantially in the two types of case.

The juvenile type.—Some of the cases recover spontaneously after a severe recurrence of the eruption every summer for several years. In others the rash becomes less with succeeding summers, and finally disappears. When once the rash has appeared it clears up very slowly, even when the patient is kept away from the sun. No treatment has had the slightest beneficial effect in any of the juvenile cases observed, beyond protecting the skin as far as possible from light.

The adult type.—The following line of treatment, based on the supposition that the toxin responsible for the sensitisation of the skin to light is of intestinal origin, has given on the whole promising results; in a very few apparent cure has been effected, in several there has been considerable improvement, and in others no benefit has accrued. Intestinal stasis has been treated by courses of Plombières douches when practicable, by the regular administration of liquid paraffin or other laxative, and by the occasional use of calomel in small doses or blue pill at night followed by an early-morning saline purgative. In cases of hypochlorhydria dilute hydrochloric acid has been given after meals. Injections of a vaccine prepared from the

intestinal organisms have on the whole appeared to be more effective than any other therapeutic measure employed. In the majority of cases a mass-vaccine prepared from all the intestinal organisms by Danysz's method, either by Professor Eyre or by Dr. F. A. Knott, has been used. The use of non-specific substances such as peptone, milk and other proteins has not in our hands proved of any service. Various changes in the diet were tried, such as excluding chlorophyll, hæmoglobin-containing foods and cereals, but without any apparent benefit. At the present time several cases are being treated with a view to changing the intestinal flora by Bacillus acidophilus therapy, and one case, at least, has given a promising result; no opinion can as yet be given, however, as to the value of this method.

Local treatment.—No local measures designed to protect the skin from light have been satisfactory. In some cases the application of an ointment or cream and a powder containing quinine has appeared to give some protection. It is of interest that quinine should protect the skin (of light-sensitive people), for this drug fluoresces a blue colour identical to that shown by normal epithelium. Hæmatoporphyrin and drugs fluorescing colours other than blue, on the other hand, tend to aggravate the condition. We have not had sufficient experience of the effect of yellow vaseline, as suggested by Peacock and MacCormac,[31] to express an opinion as to its value.

Fluorescence

A fluorescent substance exhibits selective absorption, and utilises part of the energy of the absorbed rays to generate light of a greater wave-length; that is to say, the emitted rays have a greater wave-length than those absorbed. It follows, therefore, that this property can be demonstrated particularly when the fluorescent substance is exposed to an ultra-violet beam. Now it happens that photo-sensitising substances exhibit this phenomenon to a remarkable extent; eosin, for instance, when exposed to a beam of pure ultra-violet fluoresces a deep yellow, quinine a blue-violet, and hæmatoporphyrin a crimson red. It appeared possible, therefore, that this property might be exhibited in an abnormal amount or unusual form in the skins or body-fluids of cases of light-sensitisation.

A mercury-vapour lamp was erected in a dark room, and a beam of light from this was directed through a plate of black glass, transparent to ultra-violet, but opaque to all visible rays (made by Chance Bros., Smethwick Works, Birmingham). The

substances to be tested were exposed to the ultra-violet beam, and were placed in quartz test-tubes, when fluid.

There is, in normal tissues, including the skin, a substance which fluoresces a blue colour. Bence-Jones,[29] who first demonstrated this in 1866, gave to it the name of animal quinoidine. There is no fluorescence where the epithelium is absent. This blue fluorescing substance has more recently been investigated by Kinnersley, Peters and Squires,[34] who consider that most probably it is urochrome. The same workers have been able to make blue fluorescent ether extracts from the skin, but find that the main part of the blue fluorescence is associated with a gelatine-like substance.

We also found this same fluorescence present in the serum and in fæcal extracts in high dilution.

The skins of normal individuals were examined for fluorescence, and the degree was found to vary considerably. Several cases of hydroa æstivale were also examined, and their skins were found to be particularly fluorescent. The active lesions in these cases showed up very strikingly, but it cannot be claimed, however, that this is characteristic, as the lesions in other dermatological conditions, *e.g.* eczema, not directly due to the sun, and lupus erythematosus produced a similar appearance. It does suggest, however, that damaged epithelium absorbs this fluorescing substance to a greater extent.

The urines and sera of the milder adult type under discussion, when examined for fluorescence, showed nothing unusual. Unfortunately it was not possible to obtain the urines of the two cases of hydroa vacciniforme which had previously given the minute traces of hæmatoporphyrin with the spectroscope. But the urine of a severe case of porphyria congenita, kindly sent to us by Dr. Hugh T. Ashby,[3] gave a brilliant red fluorescence. This was still demonstrable after the urine had been diluted 180 times. The same specimens, when examined with the spectroscope, lost their alkaline bands after dilution 32 times, and the acid bands after 34 times. Even when diluted with normal urine, the red fluorescence was evident in 5 times the dilution in which it could be detected with the spectroscope.

The Action of Light on the Skin

Experiments were carried out with the object of attempting to decide which rays in the solar spectrum are responsible for the various effects produced upon the normal skin, and those capable of producing the diseases under discussion. It is, unfortunately, impossible to isolate any particular band in sufficient intensity to observe its effects upon the skin. More-

over, individual susceptibility varies greatly. Blondes, for instance, are more sensitive than brunettes.

The portion of the skin selected was the inner side of the upper arm, as it is that normally most sensitive to light, and, being protected, as a rule, it is free from lesions.

Exposures were made to the carbon arc lamp and pure tungsten electrodes.

(A) *Carbon arc lamp.*—The beam was passed through a plate of glass ¼ inch thick in order to exclude the short ultra-violet rays, and intensified by passing it through a large glass lens. The distance of the flame from the skin was four feet and the exposure given was twenty minutes. In this way a maximum of visible rays was produced.

(B) *Pure tungsten electrodes.*—The beam was passed through a quartz lens and focussed on the skin at a distance of one foot. Here a maximum of violet and ultra-violet rays was obtained, the yellow and red being negligible.

(C) The same beam was used, but was passed through Chance's glass, the transmission band of which lies between 3,000 and 4,000 Angström units, with a maximum at Å. 3,650: 50 per cent. of these rays are allowed to pass and therefore twice the exposure was given. The opacity of the glass to visible rays was tested with the spectroscope and found to be completely opaque. Its transparency to ultra-violet radiation was proved by the experiments on fluorescence.

Observations were made upon normal subjects and upon cases of light-sensitiveness of both types, and the following results were obtained:

Carbon arc (maximum visible rays).—In most normal cases there was little or no reaction, although attention was frequently called, during the exposure, to the warmth of the skin. In some there was slight erythema and swelling after six hours, but little remained on the following day.

In adult cases of light-sensitisation perceptible erythema and very marked œdema were produced, which reached a maximum within twenty-four hours. Except in two cases, however, this subsided completely within seventy-two hours.

In juvenile cases of light-sensitisation the reactions produced were not in excess of normal controls, but in two cases isolated vesicles appeared on the exposed area on the following day which broke down and crusted, hæmorrhages sometimes taking place into them.

Tungsten electrodes (maximum blue-violet and ultra-violet).—Normal cases differed considerably in their response. Exposures of one, two, three, four, five minutes were given. No reaction

was obtained with the small doses; usually a slight erythema was produced in four to six hours with three minutes, but in other cases four or even five minutes were required. The erythema died down in forty-eight hours. Œdema was not produced.

In adult sensitives the results were striking. A marked erythema was produced with one minute's exposure; with two minutes this was intense, and with three minutes a number of papules developed which became vesicular, burst and crusted, producing a picture exactly resembling severe hydroa æstivale. In one instance, large bullæ, the size of a shilling, were produced. The swelling, however, was relatively less marked than with the carbon arc.

In juvenile sensitives the erythema produced was not in excess of normal people, and in one case five minutes' exposure was required for this reaction to take place. In one instance a few vesicles appeared on the following day.

With *tungsten and Chance's glass* (ultra-violet only), no reaction of any kind was obtained in normals or in any case of light-sensitisation, except a slight erythema on prolonged exposure. A fine, branny desquamation subsequently appeared on the exposed surface.

The following further experiment was performed:

A boy, convalescent from a fractured femur, and normal as far as his skin was concerned, was placed with his back exposed to a double carbon arc and tungsten arc lamp at a distance of three feet. The spectrogram of this lamp shows a very wide range of radiations from Å. 7,000 to 2,300.

Part of his back was kept bare. Other areas were covered by—

1. A trough containing quinine bi-hydrochloride 5 per cent. solution to exclude all ultra-violet rays.
2. Chance's glass to exclude all rays except the ultra-violet.
3. A piece of wood, opaque to all rays, as a control.

He was exposed for twelve minutes. The following day the bare area was markedly erythematous. The area covered by the wood, remained, of course, normal. In both the other areas there was slight erythema, and of about equal intensity.

The pigmentation which followed these exposures varied with the subjects, and with the rays used. With the carbon arc it was of a dark brown colour, with the tungsten and mercury vapour it was of a yellowish tint. On the whole the cases of light-sensitiveness pigmented more than normals. Pigmentation, then, appears to be a natural protective mechanism of the deep tissues against the longer visible and heat-rays.

It would also appear that rays of long wave-length produce chiefly œdema and pigmentation. Rays at the short end of the visible and the long end of the ultra-violet produce the maximum amount of erythema and the lesions in the adult cases of hydroa; whilst those in the extreme ultra-violet do not penetrate sufficiently to produce these results.

Conclusions

It would appear from the foregoing observations that cases of light-sensitisation may be divided into two groups.

The juvenile group.—This includes the rare and severe cases with definite hæmatoporphyria congenita reviewed by Garrod, in which symptoms and signs of the skin lesions show themselves from birth, and in which the agent at work, namely, hæmatoporphyrin, is beyond question. It also includes the rather less severe cases of hydroa vacciniforme which appear in early childhood, described by Bazin. In these porphyrins have not hitherto been looked for. We were able to find them in the urines of two cases and in the fæces of three.

The phenomenon of fluorescence furnishes us with a more delicate test for hæmatoporphyrin than does the spectroscope, and doubtless it will more often be detected in these juvenile cases by the application of this test.

Hæmatoporphyrin does not appear to be produced in these cases by the action of ultra-violet rays on red cells, as suggested by Linser, nor is it manufactured from chlorophyll or meat-fibres in the alimentary canal, as suggested by Stokvis. Fischer's contention is probably, therefore, correct, namely, that it is an intermediate product in the conversion of hæmoglobin into bilirubin, and due to an error of metabolism.

The lesions of the skin are deep, and it is probable that the blood-vessels and tissues containing hæmatoporphyrin, situated at some distance from the surface, are acted upon by rays of visible light which have considerable penetrating power.

The adult group.—The skin of normal individuals varies greatly in its sensitiveness to light, and it is certain that many cases of simple hypersensitiveness have hitherto been regarded as pathological. There is a substance, the origin and nature of which is not yet established, which is normally present in the tissues, and which can partly be extracted from the skin. This substance fluoresces a blue colour, and the degree to which it is present in the epithelium determines its sensitiveness to light. An index of this sensibility can be obtained by the degree of fluorescence observed.

But there is a very definite pathological group, the charac-

teristic clinical features of which have been already outlined. This includes the conditions variously known as Hutchinson's summer prurigo and solar dermatitis. The symptoms begin, as a rule, much later in life. In one of our cases, they did not develop until after forty years of age, and several were over thirty when the rash first appeared. No abnormal sensitising agent has been found in these cases. There is certainly no evidence that it is hæmatoporphyrin. The almost constant discovery of unusual flora in the fæces, however, aided by the very sluggish passage of food through the intestines, and the lack of hydrochloric acid in the gastric secretions, suggest very strongly that the trouble originates in the alimentary canal. The organisms isolated from these cases produced no toxin capable either of causing hæmolysis of the red cells, or the production of hæmatoporphyrin from laked blood, as was proved by their growth on special media. Again, nothing unusual is produced by the action of light on the blood or serum. It seems probable that the sensitising agent in these cases is either a decomposition product of protein or (more probably) a bacterial toxin, which, acting upon the cells of the epidermis themselves, renders them hypersensitive to light.

It cannot be stated with any accuracy exactly which rays are responsible for the various effects produced upon the skin in health and in these diseases, because it is impossible to isolate such rays in sufficient intensity to measure them. Particularly is this the case in dealing with ultra-violet radiation. It is true that, as measured by such methods as the killing of infusoria, the activity of the radiations becomes greater as the wave-length becomes shorter, but it is also true that their power of penetration is correspondingly decreased, and the undamaged skin proves an effective barrier to such action.

From the foregoing experiments it appears that the maximum effect as regards erythema is caused by waves at the short end of the visible, and the long end of the ultra-violet spectrum, that is to say, rays between Å. 3,400 and 4,400. The figures of Hausser and Vahle and Johansen are altogether too low and cannot be accepted. It is these rays which are responsible for the production of the adult type of light-sensitiveness. The radiations of longer wave-length in the visible spectrum tend more to the production of œdema and pigmentation, but when there is some abnormal sensitising agent present in the deep tissues (*e.g.* hæmatoporphyrin), the more severe cases here described may result. Rays in the extreme ultra-violet do not penetrate sufficiently to produce these effects.

No. of Case.	Age.	Age at onset of rash.	*Urine.* Indican.	*Urine.* Hæmato-porphyrin.	*Fæces.* Hæmato-porphyrin on meat-free diet.	*Fæces.* Bacteriological examination.	Alimentary x-ray findings.	Test-meal reports.	Reaction to light.		
									Carbon arc: maximum visible rays.	*Tungsten:* maximum blue-violet + ultra violet.	*Tungsten and Chance's glass:* ultra-violet only.
Adults.											
Case 1. G. E.	37	30	?	—	—	*B.c.c., Enterococci, B. coli Friedländer.*	Marked viscero-ptosis, especially cæcum.		Much swelling. Erythema. Tender.	Marked erythema 1 min.; vesicles formed 3 min.	V. slight erythema.
Case 2. J. M.	38	34	++	—	—	*B.c.c., Strep. longus* and *fæcalis.*	Moderate ptosis of transverse colon; delay.	Achlorhydria.			
Case 3. A. H.	39	26	+	—	—	*B.c.c., Strep. hæmolyticus.*		Hypochlorhydria.	V. marked swelling. Erythema. Tender.	Erythema +++ vesicles and large bullæ formed 3 min.	V. slight erythema; desquamation.
Case 4. R. K.	31	24	+	—	—	*B.c.c., Strep. longus, B. coli Friedländer.*	Normal.	Marked hypochlorhydria.			
Case 5. F. L.	40	35	—	—	—	*B.c.c., Strep. longus, B. coli Friedländer.*		Hyperchlor-hydria.	Slight swelling and redness	Erythema 1 min. marked; papules 3 min.	Nil.
Case 6. *L. N.	18	15	?	—	—	*B.c.c., Enterococcus* only.	Definite delay in transverse colon.	Achlorhydria.	Practically nil.	Normal (erythema in 4 min.).	Nil.
Case 7. K. B.	40	23	+	—	+	*B.c.c., Strep. longus, B. coli Friedländer.*	Considerable ptosis; marked delay	Complete achylia.			
Case 8. *R. C.	26	24	+	—	—	*B.c.c., Enterococcus, Strep. longus.*	Cæcum falls forward; delayed emptying.	Slight hypo-chlorhydria.	Nil.	Normal (slight erythema 3 min.).	Nil.

Case 9. H. R.	45	41	+	−	+	*B.c.c., Strep. longus.*	Marked delay; general ptosis.	Marked hypochlorhydria.	V. slight swelling, and erythema.	Erythema slightly in excess.	V. slight erythema; slight desquamation.
Case 10. D. B.	32	20	−	−	−	*B.c.c., Strep. longus* (later normal).	Definite delay: ptosis of large gut.	Normal.	Marked swelling. Erythema. Tenderness.	Erythema ++ and formation of vesicles.	V. slight erythema.
Case 11. A. C.	38	32	+	−	−	*B.c.c., Staph. aureus,* Anaërobes ++.	Normal.	Hyperchlorhydria (very slight).			
Juveniles.											
Case 12. A. A.	12	2	−	+	+	*B.c.c.* only.	V. slight coloptosis.	Normal; rapid emptying.			
Case 13. H. B.	13	4	−	−	−	*B.c.c., Enterococci* only.	Normal.	Normal; rapid emptying.	Nil.	V. slight erythema.	Nil. Slight desquamation.
Case 14. G. B.	7	4	−	+	+	*B.c.c., Enterococci* only.	Normal.	Normal.	No swelling or erythema. Papules and vesicles 2nd day.	Normal.	Nil.
Case 15. A. B.	10	3	−	−	+	*B.c.c.* only.	Normal.	Normal; rapid emptying	No swelling or erythema. Papules and vesicles 2nd day.	Slight erythema, vesicles formed.	Nil. Slight desquamation.
Case 16. B. G	10	2	−	−	−	*B.c.c., Enterococcus.*	Normal.	Vomited meal.	Nil.	Normal.	Nil.

APPENDIX OF CASES

Case A.—Mr. F. H., stationmaster, aged 37, was sent by Dr. Fisher of Fakenham to one of us (H. W. B.) on April 11, 1921, for an "eczema" which for the past three years had appeared on the face, neck, ears and backs of the hands in spring and lasted, with periodical exacerbations, throughout the summer. In winter he was quite free. He was a sallow, toxic-looking person, with bluish clammy hands; he had long suffered from constipation, for which he was in the habit of taking liquid paraffin and sometimes magnesium sulphate. The eruption, when first seen, was characteristic of light-sensitisation of the adult type, and involved chiefly the ears, the part of the neck above the collar, and the nose and malar regions. His lips were of a bluish-grey colour. *The urine* contained a faint trace of albumen, and slight albuminuria had been noted before: there was also a large excess of indican. It was thought that the albuminuria might be of static origin, but Dr. Fisher found a minute trace in an early morning specimen, and a larger quantity after a game of golf and a meal. He therefore sent a sample to the Clinical Research Association, which on culture showed the presence of *B. coli* and *Streptococcus fæcalis*. A vaccine was prepared from these organisms, and a quinine-cream and powder were given in order to afford some protection from light.

On September 3 of the same year Dr. Fisher reported that the bacilluria had apparently ceased, but that albumen was still present: during the summer three slight attacks of the eruption had occurred, the last being the result of a holiday by the sea, the lips, neck, ears and backs of the hands being chiefly involved. I saw him again on September 19; the eruption consisted of eczematous papules and patches intermingled with urticarial lesions. It was decided to admit him to Guy's Hospital for investigation.

X-ray examination of the alimentary tract showed considerable stasis throughout the colon. A mass Danysz vaccine was prepared from the intestinal organisms. Immediately after his return home (March 1922) an acute outbreak of the eruption developed after a game of golf in a cold wind and brilliant sunshine. Dr. Fisher then commenced a course of the Danysz vaccine, and internally the patient was advised to take liquid paraffin daily, and a blue pill once a week, followed by a morning saline. In August it was reported that only slight irritation had occurred in hot weather during the summer, and that he had never had to use any local application. In October the patient wrote that he had been able to play golf and tennis at the seaside without any ill effects except slight irritation over the malar regions.

Early in 1923 it was decided to give him a further course of Danysz vaccine in the hope that it might prevent or at any rate mitigate the outbreak that was likely to occur in the spring. Specimens of fæces were therefore sent to the Clinical Research

Association. Cultures gave *B. coli*, a bacillus of the Morgan group, and *Streptococcus fæcalis*, together with about 25 per cent. gram-positive bacilli, chiefly proteolytic and saccharolytic anaërobes. From these organisms a mass vaccine was prepared by Danysz' method, which was administered by Dr. Fisher. The patient reported in March of this year that, apart from slight "urticarial outbreaks" on the neck and hands, he has had no further trouble, and this "urticaria" he attributes to his not having taken the blue pill regularly. At his own request he has had no further injections of vaccine since the spring of 1924.

Comments.—This case has been reported in detail as by the intelligent co-operation of Dr. Fisher and the patient himself accurate observations were possible over a period of several years. The points of interest are—(1) the long history of constipation and symptoms of intestinal toxæmia of the putrefactive type; (2) the presence of bacilluria, which has been observed also in other similar cases; (3) the progressive improvement that followed the administration of a vaccine prepared from the intestinal organisms. It might be thought that the satisfactory result obtained was due to the regular use of laxatives and not to the vaccine, but it should be observed that the patient had already been in the habit of taking liquid paraffin and magnesium sulphate. Until we know what is the sensitising substance in these adult cases of light-sensitisation it is idle to speculate on the action of the vaccine. It is probable, however, that it acts by desensitising the skin to the light-sensitising toxin; that this action is to some extent specific is suggested by the fact that, in spite of the results published by Castle,[35] we have found that peptone has little or no effect in these cases.

Case B.—Miss K. M. F. was sent to one of us (H. W. B.) by Dr. R. Curle in February 1923 for seborrhœic dermatitis of the scalp and neck. At that time there was nothing to suggest light-sensitisation. She gave a history of constipation, alternating sometimes with attacks of flatulence and loose motions. The seborrhœic dermatitis responded to treatment, but in August 1924 she consulted me again for a typical eruption due to light-sensitisation of the adult type, involving the face, neck, the V-shaped area exposed by the cut of the blouse, and the shoulders. Her lips had the characteristic bluish tint noted in other similar cases.

She was admitted to the private ward at Guy's Hospital in October 1924 for investigation, the results of which were briefly as follows:

Fractional test-meal (Dr. Ryffel). Slight hypochlorhydria.

Urine (Dr. Ryffel). No porphyrin; no excess of pigment; no indican, albumen or sugar.

Fæces (Dr. Ryffel). No hæmatoporphyrin either on a meat-free or meat-containing diet.

Fæces (Dr. Eyre). A very abnormal stool, the predominant organism being a pathogenic "blue" coliform such as is often found in cases of chronic colitis: this organism was agglutinated by the patient's serum.

A course of Plombières douches was given, sour milk was taken for a while, and an autogenous vaccine prepared from the "blue" coliform organism was injected at suitable intervals.

In January 1925 I saw the patient again, and she informed me that after the three previous doses of vaccine (75 million) there had been a severe reaction in the light-sensitive areas. On the whole she was better both as regards her digestion and her tolerance of light. In March, however, she had a severe attack after playing golf in the sun and east wind. When seen in September the patient stated that she had passed very satisfactorily through the summer, having been able to play tennis, even in strong sunlight, without ill effects, whereas in the previous summer she had hardly ventured out-of-doors on sunny days. She went to the Riviera for the winter, where the injections of vaccine were continued. She remained almost free from any eruption until the sun became strong in January. When seen on her return in March of this year there were some eczematous patches on the face.

It has now been decided to try and change the intestinal flora by feeding with lactose and dextrin and administering cultures of the *Bacillus acidophilus*.

Case 1.—Rash began at age of 30 in spring. Suffers from indigestion, always constipated. Colon easily palpable. Typical rash on face, hands and V-shaped area on chest. Teeth good. Tonsils normal.

Treated with Plombières douches, intestinal antiseptics and vaccine from fæcal flora. Patient is improving.

Case 2.—Rash appeared at 34 after confinement. Abdomen very flabby with marked liniæ atrophicæ. Papules and eczematous lesions on face, backs of hands and lower arms. Teeth: many false, others fair. Tonsils normal.

Treatment: abdominal belt and Plombières douches; Martindale's peptone; small doses of hydrochloric acid. Temporary improvement, but rash has recurred this summer.

Case 3.—Rash began at 26 when at sea. Thyroid deficiency. Tonsils very large but not septic. Distribution on face like lupus erythematosus. Lips very typical; also backs of hands and V-shaped area on chest. Complains of much irritation. Skin markedly pigmented.

Treated with vaccine from fæcal flora and high colon wash-outs.

Case 4.—Rash began at 24. Indigestion for many years. Constipated. Tongue very flabby. Rash reappears every spring and lasts through summer. Free in winter but skin remains harsh and thick.

Treated with autogenous fæcal vaccines and colon wash-outs. Marked improvement.

Case 5.—Rash began at 35 on exposed parts. Teeth false. Tongue does not suggest hypochlorhydria. Feeble peripheral circulation. Urine : albumen slight trace.

Treatment : peptone (Martindale's); paraffin; autogenous fæcal vaccine. No improvement.

Case 6.—Rash began at 15 when at the seaside. Recurs every summer. Slight anæmia (red cells 4,200,000). Admitted to hospital. Rash cleared up, but reappeared on exposure to the sun on balcony for a few hours.

Treatment : dilute hydrochloric acid and high colon wash-outs. Patient now apparently well.

Case 7.—Has always been sensitive to the sun, but first attack of hydroa was at the age of 23 while at the seaside. Suffers from fibrositis pains and flatulence. As this patient had complete achlorhydria, a duodenal tube was passed, and the bacteriology of the small intestine examined. On culture, only small quantities of *Staphylococcus albus* were grown. The gall-bladder bile gave identical findings.

Treatment : autogenous vaccines, hydrochloric acid and colon wash-outs. Marked improvement last year, but relapse (not so severe) this spring.

Case 8.—Rash began at 24. Recurs every summer. Complains of indigestion. Sallow complexion. No anæmia. Constipated.

Treatment : vaccines (autogenous), colon wash-outs and hydrochloric acid. Patient was free from rash last summer.

Case 9.—Rash began at 41. Very severe eruption on face and backs of hands. History of dysentery, with several recurrences. Suffers also from migraine. Tonsils septic, and the *streptococcus* isolated from these, when tested against patient's serum, gave a positive agglutination of 1 : 20. Organisms from this were included in fæcal vaccine.

Treatment : abdominal belt; dilute hydrochloric acid; autogenous fæcal vaccine. Considerable improvement.

Case 10.—Rash began at 20 when at the seaside. Recurs every summer and getting more severe. Teeth good, but tonsils large and septic. These were removed, but with no beneficial effect upon the eruption. Rash quickly cleared up in the ward, but instantly reappeared on further exposure to the sun.

Treatment : colon wash-outs and fæcal vaccines. Patient was free from lesions last year, but rash reappeared this spring.

Case 11.—Rash began at 32, after bathing and sitting in the sun. Recurs every summer. Eyes particularly swollen. Eczematous lesions on face, V-shaped area on chest and backs of hands. Lips typical. Pigmentation marked. Slight hypochlorhydria.

Treatment: sodium bicarbonate and sodium citrate; colon wash-outs. No improvement.

Case 12.—Always sensitive to light, but worse last year after influenza. Rash on face, backs of hands and knees. Old scarring evident. Eczematous lesions and hæmorrhage into some of the eruptions. Rash cleared up very slowly in the ward and not completely. No improvement.

Case 13.—Always sensitive to light, but some years worse than others. 1922, admitted to an Infirmary for three months. 1924, admitted to hospital, condition fairly severe, and improved very slowly on being kept away from the sun. 1925, no rash whatever, old scarring evident.

Case 14.—Two brothers died of "marasmus." One premature birth. Always had rash on exposed parts. 1923, papules, vesicles and bullæ, with hæmorrhages into some of these. 1925, eruption not so marked as formerly.

Case 15.—Always sensitive to light. Severe rash noticed at three years. Face: severe vesicular eruption. Scarring, also backs of hands and wrists. Covered parts entirely free. Investigations: negative results.

Case 16.—First rash appeared at two years of age. Face covered with vesicular lesions into which hæmorrhage has often taken place. Forehead, which is covered by "fringe" of hair, is completely free. Condition cleared very slowly in the ward.

Case 17.—Began at 32. Inclined to have flatulence with loose motions. Considerable amount of mucus found in watery offensive stools. Hypochlorhydria. Typical severe light-sensitisation, adult type.

Treatment: Plombières douches; vaccine from blue coliform organisms in fæces. Patient apparently well this year.

Case 18.—Began at 29. Rash on face and backs of hands. Very seborrhœic scalp. Complains of dyspepsia and malaise. Is a vegetarian. Hypochlorlydria. Delay in colon.

Treated with HCL and intestinal antiseptics.

Case 19.—Began at 30. Rash on exposed parts. Much swelling round the eyes. Marked hypochlorhydria. Chronic colitis. Passage of intestinal cast.

Treatment: liquid paraffin; HCL; peptone injections. Some improvement.

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THE SIGNIFICANCE OF THE RESPIRATORY QUOTIENT

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In these days there is an increasing application of physiological work to the problems of disease, and clinicians have shown a special interest in respiratory exchange in relation to basal metabolism, diabetes and goitre. The measurement of the absorption of oxygen and the discharge of carbon-dioxide affords a reliable indication of the exchange of material, which is a fundamental characteristic of all forms of life. Numerous observations have been made upon the subject from the quantitative point of view and much has been written about basal metabolism in relation to so-called standards or normals. This aspect will not be considered in this paper, but we would wish to insist upon the wide range of variations in different healthy subjects and the danger of a rigid acceptance of standards or normals: what is a sign of health in one man may be a sign of disease in another.

There is another aspect of respiratory exchange, the relationship of the volume of oxygen absorbed to the volume of carbon-dioxide discharged, which is important on account of the light it throws upon the nature of the chemical processes occurring in the body. This respiratory quotient has been the subject of much research and debate, and in this paper an attempt will be made to review the position and give the results of further experiments made in this laboratory.

It is now generally agreed that the respiratory quotient is to be regarded as the resultant of varying quotients due to chemical changes in the different organs of the body. This resultant will be of great complexity, for not only the oxidation of each molecule of protein, fat, or carbohydrate used by the organism, but also any transformative change in which these molecules take part will be represented in the final quotient.

The view that the respiratory quotient is composed only of varying contributions from the combustion of the three chief

classes of food (0·7 fat, 0·8 protein, 1·0 carbohydrate) * is no longer tenable. Numerous experiments have shown that quotients above and below the values of 0·7 and 1·0 occur in certain conditions. Such quotients must indicate the influence of processes which contribute factors below 0·7 and above 1·0 to the final figure. The marked effect of these processes emerges when the respiratory exchange is examined under the special conditions of fasting, hibernation and fattening. Thus a transformation of carbohydrate to fat explains the high quotients observed in the fattening of animals, while the reverse change accounts for the low quotients found in fasting and hibernation. In the first case, Hanriot suggested that a considerable quantity of carbon dioxide is split off from the carbohydrate molecule and is discharged as carbon dioxide, the oxygen of which was derived from the intramolecular oxygen of the food; in the second case, Voit and Chauveau held that fat underwent a partial combustion, sugar was formed and stored up as glycogen in the liver and muscles. Hibernating animals possess a large deposit of fat which disappears during the period of torpidity, and during this time, as Bernard showed, glycogen accumulates in the liver.† Further, there is evidence that these processes are not confined to the special states of the animal in which their influence on the total quotient is most marked; it appears from examinations of the influence of work on the respiratory quotient that such transformative activities are in progress also during periods of normal feeding, when their influence is overshadowed by that of the catabolic factors. An examination of the tabular material used in the main clinical application of the respiratory quotient indicates that the true composite nature of the quotient is not fully realised, and that a rigid conception based on the three catabolic factors still prevails, quotients below 0·7 or above unity being regarded as due to experimental error.

In clinical examinations of the metabolism by the method of indirect calorimetry the patient's respiratory exchange and

* 1. *Fat*, $C_3H_5(C_{18}H_{33}O_2)_3 + 80O_2 = 57CO_2 + 52H_2O$.

$$\text{Olein, R.Q.} = \frac{CO_2}{O_2} = \frac{57}{80} = 0{\cdot}71.$$

2. *Carbohydrate*, $C_6H_{12}O_6 + 6O_2 = 6CO_2 + 6H_2O$.

$$\text{Dextrose, R.Q.} = \frac{CO_2}{O_2} = \frac{6}{6} = 1{\cdot}0.$$

3. *Protein*, $C_{72}H_{112}N_{18}O_{22}S + 77O_2 = 63CO_2 + 38H_2O + 9CO(NH_2)_2 + SO_3$.

$$\text{Empirical albumin, R.Q.} = \frac{CO_2}{O_2} = \frac{63}{77} = 0{\cdot}82.$$

† See Equation, p. 348.

quotient are determined by measurement and analysis of the expired air, and in order to express the result in terms of calories, it is customary to refer to certain tables which purport to give the heat produced by the combustion of a litre of oxygen at various quotients. An estimate of the heat production is then based on a combination of the readings from these tables with the oxygen intake. The table quoted in most medical text-books [1] is taken from the work of Zuntz and is as follows:

Respiratory Quotient.	*Calories per Litre of Oxygen.*
0·75	4·74
0·80	4·80
0·85	4·86
0·90	4·92

It is to be noted that this table provides the heat equivalent of only four values of the respiratory quotient within a narrow range, and, moreover, the equivalents are calculated on the assumption that fat and carbohydrate only are broken down. It is known, however, that protein is undergoing metabolism and that carbohydrate can be converted into fat. There is also evidence, disputed it is true, that fat may give rise to carbohydrate. We have made use of this table to calculate the heat output from data given in previous work, and compared the result with that of calculations in which the protein breakdown was taken into account. Such a comparison shows that the use of the tables must introduce not less than a 5 per cent. error. Even so, reference to the tables is to be preferred to the method of assuming a quotient round about the supposed normal figure, a procedure which is only too prevalent.

The study of the respiratory quotient in diabetes and anæsthesia is very incomplete and will receive only brief consideration here.

The present work consists of a series of determinations of the respiratory quotient made on animals under controlled conditions as regards fasting and feeding. Observations on animals have the advantage that the condition of the experiment may be controlled more efficiently than is the case with man. It would be almost impossible to make a large series of observations on human subjects who have fasted for two or three days, and in using animals we have the additional advantage of being able to avoid some of the errors inherent in methods applicable to the human subject. There is, moreover, no evidence that fundamental differences are found in the metabolism of man. Haldane's modification of the Pettenkofer and Voit apparatus for the determination of the respiratory exchange

provides a means whereby quotients can be obtained from animals with a reasonable degree of accuracy. A mathematical analysis of the results based on the assumption of a maximum error of 0·02 grm. in weighing showed the maximum error in the quotient to be $\pm$ 0·02. The balance used may be considered accurate to ·01 grm., if the weighings are made with reasonable care. During the experiments the animal is under conditions as similar as possible to those of its cage, and a preliminary period of half an hour in the ventilated chamber ensures time for adaptation.

The following results consist of recent determinations (E. T. C.) and a series not previously published (M. S. P.), but carried out as controls for work now in progress on the effects of anæsthesia upon the respiratory exchange.

In the tables the respiratory exchange is expressed in grammes per hour, but in every case in which the period of

TABLE I.

WELL-FED RABBITS.

Date.	Wt. of animal.	Rectal temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
12.11.09	1617			1·27	1·71	1·33	No. 1. No urine, no fæces during experiment.	0·93
13.11.09	1620		15·6	0·86	1·76	1·20	No. 1. No urine, no fæces : ½ hour × 2.	1·07
15.11.09	1670		17·5	1·33	2·04	1·54	No. 1. No urine, 1 pellet: ½ hour × 2.	0·96
16.11.09	1663	37·5	17·0	0·86	1·64	1·40	No. 1 . . . ½ hour × 2	0·85
20.11.09	1525			0·92	1·76	1·28	No. 2 . . . ½ hour × 2	1·00
23.11.09	1535			1·14	2·18	1·62	No. 2 . . . ½ hour × 2	0·98
2.12.09	951			0·62	1·20	0·84	No. 3 . . . ½ hour × 2	1·04
3.12.09	882			0·76	1·30	0·76	No. 4 . . . ½ hour × 2	0·86
11.1.10	1042	39·0		0·90	1·58	1·30	No. 5. ♂. No urine, no fæces . ½ hour × 2	0·88
17.1.10	1007			1·34	1·88	1·36	No. 5. ♂. . . . ½ hour × 2	1·00
18.1.10	1643			1·46	1·74	1·40	No. 6 . . . ½ hour × 2	0·90
18.10.11	488	39·2	17·0	0·70	1·35	1·01	No. 7. Young.	0·97
14.11.11	1201	39·5		0·82	1·81	1·36	No. 8.	0·97
15.11.11	1180	39·5		0·79	1·55	1·26	No. 9.	0·90
6.1.14	2160			1·02	2·35	1·73		
				1·02	2·35	1·73	No. 10. Three-hour period. No urine during experiment.	0·99
		38·8		1·02	2·35	1·72		
27.11.14	1930			1·38	2·79	2·03	No. 11. ♀ Consecutive periods.	1·00
	1927	38·5		1·24	2·72	1·90	No. 11. ♀ Consecutive periods.	1·04
1.12.14	1981	38·7		1·57	2·54	1·86		0·99
				1·56	2·54	1·85	No. 11. ♀. Some fæces and urine passed during experiment. Two-hour period.	
3.12.14	1909			1·24	2·45	1·81	No. 12. ♀. No urine, no fæces	0·98
	1907	38·5		1·20	2·31	1·71	No urine, no fæces *	0·98
4.12.14	2013	39·0		1·46	2·72	1·98	Urine passed.	1·00
10.12.14	2000	39·0		1·44	2·78	2·02	No urine, no fæces.	1·00
17.12.14	2090			1·51	2·91	1·97		1·08
22.12.14	2054	39·0		1·54	2·07	1·56		0·96
9.11.25	1704		14·0	0·66	1·73	1·36	No. 13. ♀. No urine, no fæces. 1½ hours × ⅔.	0·93
23.11.25	1740	38·3	14·5	0·83	2·12	1·65	No. (14).†	0·93
27.11.25	1830	38·6	14·0	0·64	1·63	1·16	No. (15). Restless.	1·02
13.3.26	1990	36·6	14·5	1·17	2·04	1·67	No. (16).	0·88
26.4.26	2325	39·0	14·5	1·48	3·58	2·48	No. (17). Fæces passed.	1·05
4.5.26	2543	39·8	15·0	0·71	2·69	2·15	No. (18).	0·90
12.5.26	2460	37·8	13·0	1·17	3·40	2·56	No. (19).	0·96
25.5.26	2360	37·8	16·5	1·66	4·01	2·87	No. (20). Restless.	1·01
1.6.26	1710	38·5	16·5	1·60	2·66	2·08	No. (21).	0·93

* Consecutive periods.

† The determinations for the animals, the numbers of which are in brackets, were made by E. T. C.

observation was longer or shorter a note to that effect is given. The animal was weighed in the closed respiratory chamber, and a dummy chamber was used as a counterpoise to ensure more accurate weighing, but in the tables the decimal weights have been omitted in order to save space. The output of moisture is complicated in a few cases by the passage of urine or fæces during the experiment. The animals were ones upon which no experiments had been made previously. The temperature of the animal was taken in the rectum, except in the case of the hibernating mammals, in which it was observed by placing the thermometer against the skin of the abdomen in the coiled-up condition of the animal.

TABLE II.

FASTING RABBITS.

Date.	Wt. of animal.	Rectal temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
22.2.26	1610	37·6	14·0	1·01	1·91	1·74	No. (22).	0·79
8.3.26	2109	37·5	14·1	1·58	1·76	1·86	No. (23).	0·69
16.3.26	1880	37·0	14·0	0·80	1·71	1·69	No. (24).	0·74
22.3.26	1910	36·0	14·2	1·64	2·14	2·15	No. (25).	0·72
12.4.26	1523	36·0	14·0	0·73	1·84	1·75	No. (26).	0·76
12.4.26	2133	38·2	30·0	1·53	2·86	2·64	No. (27). Chamber warmed to 30° C.	0·78
20.4.26	1601	38·0	14·0	1·06	1·88	1·71	No. (28).	0·79
20.4.26	1925	38·0	14·5	1·46	2·15	2·25	No. (29).	0·69
27.4.26	1740	38·0	14·5	1·37	1·86	1·86	No. (30).	0·73

TABLE III.

HIBERNATING MAMMALS.

Hedgehogs.

Date.	Wt. of animal.	Temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
18.3.26	410	33·0	14·5	0·64	0·88	0·85	*Hedgehog I. Awake. Food had been supplied. 3 hours × ½.	0·75
10.4.26	390	19·0	15·0	0·48	1·06	1·13	*Hedgehog I. Uncoiled. Awakening. Fasting for 22 days.	0·68
17.11.25	657			0·58	0·93	0·89	Hedgehog II. Awakening. Temp. in coiled animal 32·0° at end of period of 3 hours. 3 hours × ½.	0·75
19.3.26	710	35·0	14·5	0·38	1·03	0·96	*Hedgehog III. Awake. 2 hours × ½.	0·78
31.3.26	690		17·0	0·86	1·20	1·13	Hedgehog III. Awakening. Fasting for 12 days. Temp. in coiled animal 14·5° at beginning, 33° at end of period. 3 hours × ½.	0·78
15.4.26		34·0	17·0	0·86	0·84	0·91	Hedgehog III. Awake. Fasting for 27 days. No urine, no fæces.	0·67
16.4.26	500		15·5	0·38	0·06	0·13	Hedgehog IV. Fasting for 27 days. Coiled up. Temp. in coiled body 17° at beginning and 16·5° at end of determination. 2 hours × ½.	0·34

Marmots.

Date.	Wt. of animal.	Temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
25.3.04	790	11·0	10·2	0·44	0·10	0·17	Animal cold. Respiration shallow. 4½ hours.	0·43
28.3.04	700	12·0	11·0	0·62	0·33	0·37	Shallow respiration. No fæces, no urine. 5½ hours.	0·65
4.04	694	35·0	12·0	0·26	0·85	0·83	Animal awake. No fæces, no urine. 1 hour.	0·74

TABLE IV.

EXPERIMENTS ON ANÆSTHETISED ANIMALS.

A. Well-fed rabbit under urethane.*

Date.	Wt. of animal.	Rectal temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
1.6.26	1710	38·5	16·5	1·60	2·66	2·08	Well-fed prior to urethane.	0·93
1.6.26	1680	35·0	16·5	0·79	2·24	1·77	Fourth hour of anæsthesia.	0·91
2.6.26	1605	35·0	16·5	0·91	1·42	1·60	After 23 hours under urethane.	0·65
2.6.26	1590	31·0	16·5	1·06	1·42	1·35	After 30 hours—recovery.	0·76

B. Fasting rabbit under urethane.*

Date.	Wt. of animal.	Rectal temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
25.3.26	1870	37·0	14·5	0·35	1·37	1·17	Fasting prior to urethane.	0·80
25.3.26	1855	33·0	14·5	0·83	1·32	1·44	Fifth hour of anæsthesia.	0·66
26.3.26	1810	33·0	14·5	1·40	1·21	1·18	After 23 hours—recovery.	0·75

C. Rabbit before and after chloral (M. S. P.).

Date.	Wt. of animal.	Rectal temp.	Air temp.	H_2O.	CO_2.	O_2.	Remarks.	R.Q.
19.11.09	1579	39·0	13·5	0·90	1·52	1·28	Prior to chloral.	0·87
19.11.09	1578	35·5	13·5	0·60	1·23	1·16	First hour after 1 gm. chloral.	0·77
19.11.09	1576	38·0	13·5	0·73	2·17	1·82	Fourth hour—recovery.	0·86

* Determinations by E. T. C.

Consideration of the Results of the Present Experiments.

An examination of Table I shows that in two series of observations on well-fed rabbits the respiratory quotients varied from 1·08 to 0·85 in twenty-eight determinations (by M. S. P.) on thirteen animals, and from 1·05 to 0·88 in eight determinations (by E. T. C.) on eight animals. This range agrees with that found in a previous investigation (Pembrey and Gürber,[2] in which eleven observations on six rabbits gave a range from 1·07 to 0·87. The explanation of these high quotients is to be found in the transformation of carbohydrate into fat. An equation which somewhat crudely represents this change is :

$$13C_6H_{12}O_6 = \underset{\text{(Oleo-Stearo-Palmitin)}}{C_{55}H_{104}O_6} + 23CO_2 + 26H_2O.$$

This view is now generally accepted, although in the past it received much opposition, the results being attributed to errors of experiments.

Table II shows that in nine observations (by E. T. C.) on nine animals the respiratory quotient in fasting rabbits may vary from 0·79 to 0·69. These results are in agreement with experiments made upon rats in a previous research (Pembrey and Spriggs).[3] In these experiments the fast was a relatively short one and the alimentary canal might still contain some food material. Prolonged fasting is a natural process in hiber-

nating mammals; for this reason further experiments on hedgehogs and marmots are given in Table III. Three observations on three fasting hedgehogs show quotients varying from 0·68 to 0·34, the quotients obtained from the same animals when feeding lying between 0·75 and 0·78. Two observations on the marmot show quotients of 0·65 and 0·43 during hibernation, results which agree with previous work.[4] Further, the sharp rise in the quotient which takes place during the awakening from the prolonged sleep is shown in other experiments recorded in this table.

An explanation of these low quotients was advanced originally by Chauveau, who suggested that they were to be accounted for by a change of fat into carbohydrate; he held that fat did not undergo direct combustion, but passed through a stage of carbohydrate. Such a change may be illustrated by the following equation, the respiratory quotient of which is $\frac{CO_2}{O_2} = \frac{18}{64} = 0{\cdot}28$.

$$2C_3H_5(\underset{\text{(Olein)}}{C_{18}H_{33}O_2})_3 + 64O_2 = 16C_6H_{12}O_6 + 18CO_2 + 8H_2O.$$

This view was contested strongly by some physiologists, notably by Krogh [5] and Graham Lusk.[6] Recently, however, Krogh and others [7] appear to have changed their views and accept the theory that fat may be transformed into carbohydrate in the animal body, as it undoubtedly is in the seeds of some plants.

The fact that in diabetes none of the sugar in the urine can be traced definitely to fat has proved a stumbling-block to many, and forms the basis of vigorous opposition from Lusk and his followers. Recent work, however, indicates that these grounds for objection are tenable no longer. It is therefore surprising to find an uncompromising denial of the conversion of fat into carbohydrate in the recent Oliver-Sharpey Lecture by Maclean.[8] As the evidence accumulates from various sources it becomes more and more probable that only on the basis of a transformation of fat to carbohydrate can the very low and the ordinary respiratory quotients be explained. Very low quotients have been found in observations upon the respiration of seeds during germination, a condition in which the conversion of fat into carbohydrate is unquestioned. It has been, and still may be, maintained that evidence from plants does not apply to animals. Such an objection has much less force in these days, for evidence increases to show that there are no fundamental differences between animals and plants.

It is to be recalled that the view that carbohydrate was converted into fat in the animal body was severely contested on chemical grounds until it was established by the crucial experiments of Gilbert and Lawes. Such a final experimental confirmation is wanting at the present time in the case of the transformation of fat into carbohydrate, but the balance of evidence is in its favour.

During anæsthesia there are changes in metabolism which need investigation from both the practical and the theoretical point of view, for there is clinical and post-mortem evidence of a disturbance in the metabolism of fat and carbohydrate. A few examples are given in Table IV of the results obtained in a research in progress on the effects of anæsthesia upon the respiratory exchange. The quotients vary from 0·93 to 0·65 in ten determinations on three animals. The lowest values of the quotient appear to be associated with a torpid condition of the animal in which its temperature falls; this state has been compared with hibernation or even termed "artificial hibernation." The rise in the quotient as the animal recovers from the anæsthesia is interesting in this connection, for no food was taken by the animals.

Previous Work upon the Subject.

It is unnecessary to give here an account of the extensive literature upon the subject, for one of us has discussed it in former papers, and recently Geelmuyden [9] has published a monograph *Die Neubildung von Kohlenhydrat im Thierkorper*, in which is given a full bibliography.

Conclusions.

The following conclusions are drawn from this extension and confirmation of previous work:

The respiratory quotient is a resultant of many factors; as such there must be components above 1·0 and below 0·7 even in the cases in which its value approaches 1·0, 0·8 or 0·7.

The component above 1·0 can be explained by the conversion of carbohydrate into fat.

The component below 0·7 can be explained by the conversion of fat into carbohydrate.

If these chemical changes are due to the action of enzymes, this will represent an extension of the general law that all processes catalysed by enzymes are reversible.

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CASE OF HYPERTROPHIC GASTRITIS (GASTRITIS POLYPOSA): RECOVERY AFTER GASTRECTOMY

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital, with Pathological Report by ADRIAN STOKES, D.S.O., M.D., Sir William Dunn Professor of Pathology, Guy's Hospital.

THE following case deserves detailed description, as I have been unable to find any reference to the condition in English literature, and in only one of the three similar cases published in French and German was any clinical investigation carried out.

Clinical History

Mr. R., aged 36, was admitted to New Lodge Clinic on March 30, 1926. He had contracted dysentery in 1917 whilst fighting in East Africa, and was discharged from the service on account of anæmia, but he continued to live in the tropics. His health improved for a time, but in November 1918 he began to have attacks of vomiting between 4 and 6 p.m., and between 2 and 3 a.m., and passed loose stools first thing in the morning. The vomiting and diarrhœa improved with careful dieting, but nausea persisted.

In 1921 he came home on account of increasing fatigue and dyspnœa, and he was treated for anæmia. He returned to Africa, and with some difficulty continued at his work and even did big-game shooting. In 1924 he was less fit again, his complexion became yellowish, his hair came out, and his nails cracked. In May 1925 he returned to England and was treated with a streptococcal vaccine prepared from his stools. His red corpuscles then numbered 3,990,000 per cub. mm., his hæmoglobin percentage being 65; in October 1925 the figures were 3,900,000 and 60 respectively.

On admission in March 1926, the x-rays showed a constant and well-marked irregularity on the greater curvature of the stomach (Fig. 1). Although nothing abnormal had previously been felt in the abdomen, when palpation was guided by the x-rays the gastric deformity was found to correspond with a definite and very tender tumour high up under the left costal

margin, which only became easily accessible on taking a deep breath. The x-rays showed that the stomach emptied itself with extreme rapidity, deep peristaltic waves passing from a point immediately distal to the tumour up to the pylorus.

A fractional test-meal showed that complete achlorhydria was present, and the last fraction contained fresh blood. The evacuation of the stomach was again extraordinarily rapid, no

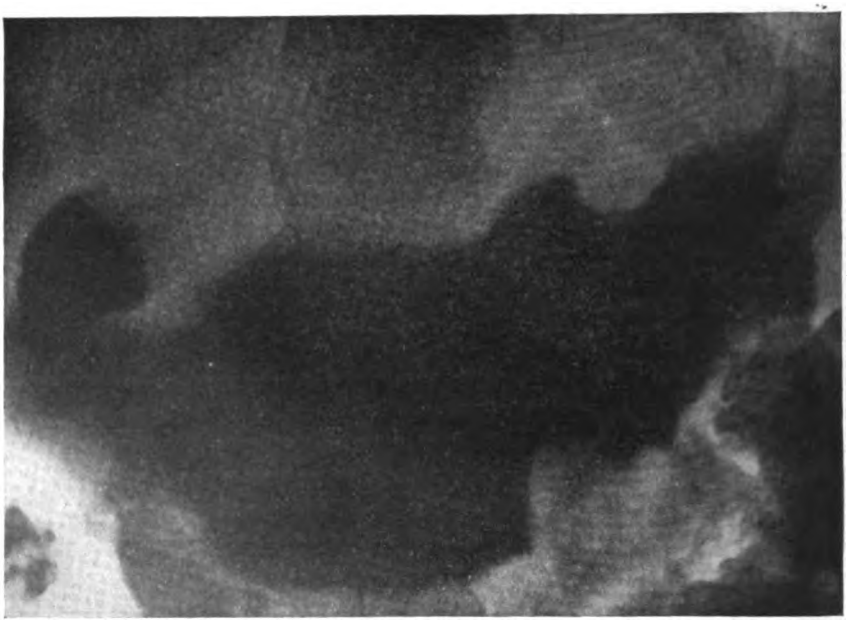

FIG. 1.

Radiogram of stomach in case of hypertrophic gastritis, showing very irregular outline caused by polypoid formation of mucous membrane (my paper on hypertrophic gastritis).

starch being present in the fraction removed a quarter of an hour after the gruel was given.

Though the first stool obtained contained no occult blood, later stools contained sufficient to give a hæmatoporphyrin spectrum as well as a positive guaiac reaction.

A serious degree of anæmia was present. The red cells numbered 3,420,000 per cub. mm., a smaller number than any which had hitherto been recorded for the patient, and the hæmoglobin percentage was 44. There was a good deal of poikilocytosis, anisocytosis and polychromasia. The leucocytes numbered 9,400 per cub. mm., with a normal differential count.

Van den Bergh's test was negative, showing that the anæmia was not hæmolytic.

The Wassermann reaction was negative; otherwise a gumma of the stomach might have been suspected in view of the long history. In spite of the history a growth of the stomach was diagnosed, but it was suggested that perhaps the long-standing anæmia might be an independent condition. Mr. L. Bromley operated on April 18. He found that the wall of the proximal two-thirds of the stomach was thick and the vessels on the outside were injected, the surface being uneven. It did not, however, feel like a growth, and we were greatly puzzled as to what the condition could be. The stomach was obviously very abnormal, and as the disease present appeared almost certainly to be the cause of the patient's anæmia, the whole stomach, with the exception of a very small area in the neighbourhood of the cardia, was removed.

The patient's convalescence was much delayed by a serious attack of left-sided pleurisy; clear fluid was aspirated on three occasions. By the beginning of July considerable improvement had taken place, though on June 9 the red corpuscles still only numbered 3,600,000 per cub. mm., and the hæmoglobin percentage was 51. The number of leucocytes had fallen to 6,400 per cub. mm., owing to a diminution in the number of polymorphonuclear cells, which formed 58 per cent. of the whole, the small lymphocytes being 32 per cent.

Occult blood had now completely disappeared from the stools, which showed no excess of starch, but some excess of fat, mostly as fatty acid and soap, and numerous muscle fibres, many of which had retained their striation. Before the operation undigested muscle fibres and starch had been present, but fat digestion appeared to be normal. As the digestive power of the stomach must already have been entirely lost, the changes observed after gastrectomy are difficult to explain.

Pathological Report

The specimen was received direct from the operating theatre, having been opened along the greater curvature. Practically the whole stomach had been removed.

When spread out, the extreme length and breadth were, respectively, 29 cm. and 19 cm. The thickness was not measured until after fixation in formalin. Considerable shrinkage took place in the process, but, on account of the mobility of the mucosa, measurements before fixation were impracticable. The measurements obtained after fixation were as follows :

Cardiac end.	Whole thickness to the summit of the convolutions	1·60 cm.
	Peritoneal and muscular coats .	0·65 cm.
	Mucous and submucous coats . .	0·95 cm.
	Mucous and submucous coats in the sulci	0·35 cm.
Pyloric end.	Whole thickness	0·78 cm.
	Muscular coat	0·40 cm.
	Mucous and submucous coat at point where convolutions were absent .	0·38 cm.

The internal aspect of the stomach showed extreme convolution of the mucous membrane with deep sulci separating polypoid projections of hypertrophied mucosa (Fig. 2). The appearance suggested the external surface of the brain, stripped of the meninges, with the convolutions unusually small and very tightly packed together. The colour was a greyish-yellow; at many points small superficial hæmorrhages had occurred; these were one to two millimetres in diameter and were situated at the summits of the folds. A thin layer of mucus covered the pyloric region; this was less evident in the body of the stomach and not seen near the cardiac end.

The corrugation of the mucosa was most prominent near the cardia; in the body of the stomach the elevations were more closely packed and smaller, and towards the pylorus the mucosa flattened out with only small elevations here and there, but still showing evidence of great hypertrophy and indications of the spread of the polypoid condition. The normal longitudinal folds, greatly hypertrophied, were present along the lesser curvature in the pyloric region. The mucosa was extremely mobile; this was most noticeable towards the cardia, and at the pyloric end the mobility approximated to normal.

No genuine polypi were present, there being no pedunculated or sessile masses of mucous membrane, but, none the less, the whole appearance suggested a mass of closely packed polypi, which had failed to develop stalks on account of their close proximity.

The peritoneal surface showed some thickening with small, rough, fibrous projections, some of them bright red in the fresh state. These were found on both surfaces of the stomach. The peritoneal attachments were normal and no enlarged glands could be found.

Blocks were cut from five areas, embedded in paraffin, and sections stained by various methods. In the sections of the

cardiac end the outstanding feature was the extreme hypertrophy of all the structures and the relatively slight evidence of

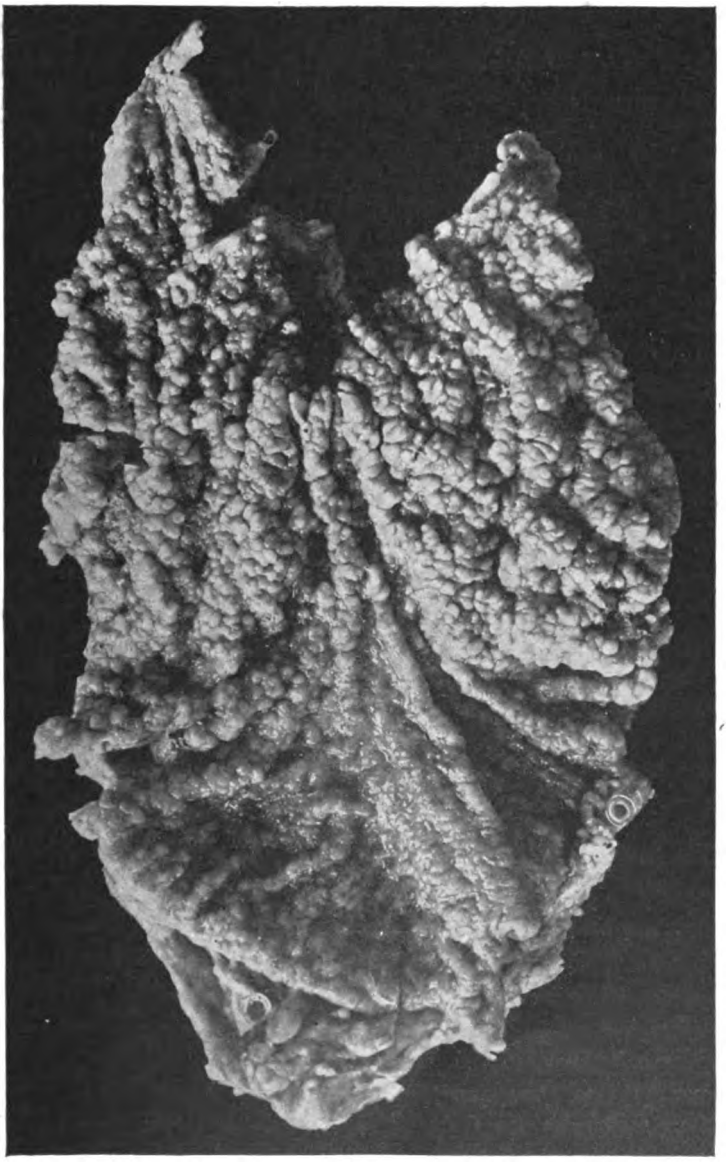

FIG. 2.

Excised stomach photographed after fixation. Reduced one half.

inflammatory changes. The supporting stroma of the glands was much increased, and with van Gieson's stain it was possible to trace strands of muscle fibres, derived from the muscularis

mucosæ, to the level of the mouths of the glands. A few wandering cells were present, but the signs of inflammation were much less evident than in other areas.

The epithelium was normal, and there were about the usual numbers of oxyntic cells in spite of the achlorhydria which had been found. The muscularis mucosæ showed great hyperplasia; it was possible to count fifteen to eighteen muscle nuclei in a direct line of breadth. The muscular coats were also very much thickened, the circular fibres showing hyper-

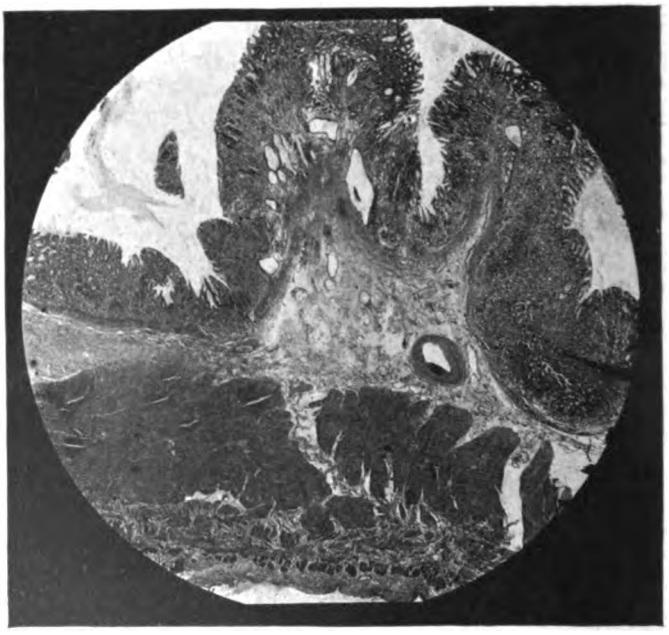

FIG. 3.
Microphotograph of stomach near cardiac end. × 12 diameters.

plasia and hypertrophy in all the areas examined. The serous coat and the underlying connective tissue were thickened, but there was no evidence of cell infiltration.

The sections examined from the body of the stomach showed changes identical with those described, but superimposed on them there was clear evidence of subacute inflammation. The mucosa was everywhere invaded with large numbers of wandering cells; these were found at the base of the glands and right to the extremity of the ducts. They were in large groups at the base of the glands and closely packed between the epithelial cells along the vessels. The cells varied in different groups; sometimes the majority were plasma cells (Pappen-

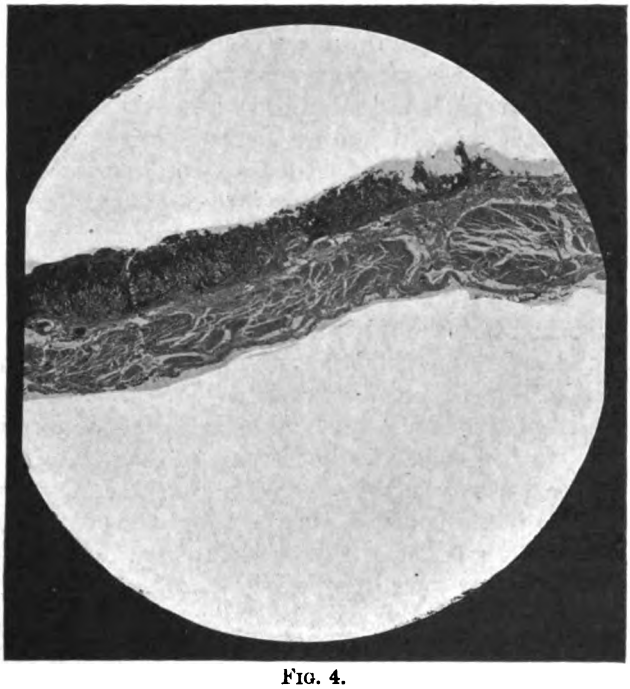

FIG. 4.

Microphotograph of normal stomach to compare with Fig. 3. × 12 diameters.

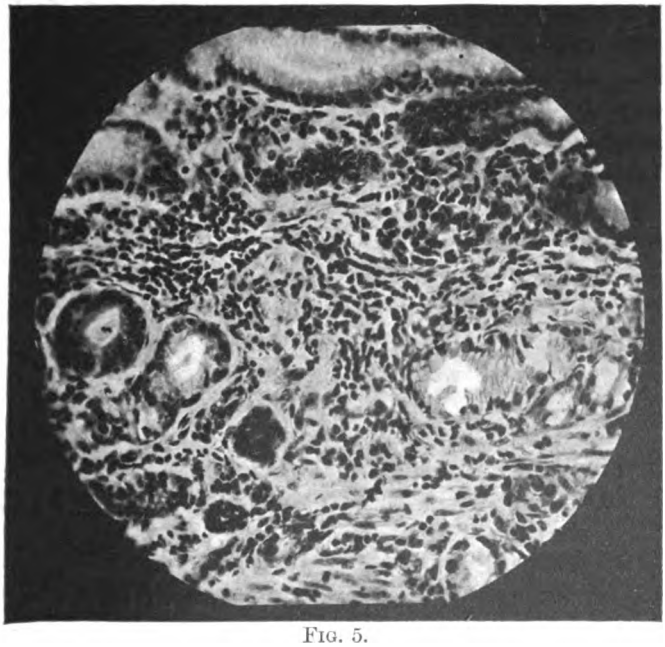

FIG. 5.

Microphotograph of mucous membrane, showing cell infiltration. × 225 diameters.

heim's stain), and in other groups there were many eosinophil cells, and sometimes the cells were about evenly mixed; numerous lymphocytes were present and a few polymorphonuclears were found. The epithelium was normal in appearance, no excess of goblet cells being demonstrated with muci-carmine. Small collections of wandering cells were found around the vessels in the submucosa, the majority being plasma cells. There was no excess of lymph follicles. The supporting connective tissue of the submucosa was thin and loose; it appeared as if it had become stretched and loose, and as a result of shrinkage had become folded on itself.

Some of the larger vessels showed arteriosclerotic changes; this is clearly seen in the illustration (Fig. 3). The muscular coats were hypertrophied, but here and there small groups of cells were seen and occasionally fibrous patches.

The sections from the pyloric region showed less evidence of inflammation, but in all other respects the changes were identical with those found in the other regions.

The ganglia everywhere appeared normal. Bacterial stains failed to reveal any organisms in the mucous or submucous coats, though about the usual numbers of bacteria were found on the surface of the mucous membrane.

To summarise, there was hyperplasia and hypertrophy of all the coats, most evident in the mucous coat at the cardiac end; there was clear evidence of subacute and chronic inflammatory changes in the mucosa, best seen in the body of the stomach; there was no evidence of tumour formation; there was no metaplasia of the epithelium. It would seem that the condition was one of extreme hypertrophic gastritis, and that, although the changes found agree very closely with the description of "gastritis polyposa" given by Meulengracht,[1] the absence of definite polypi precludes the use of the latter term. The conditions are essentially the same, and the development of polypi probably depends on more strictly localised inflammatory areas giving rise to hypertrophy of the mucosa, which becomes polypoid or sessile owing to the absence of lateral support.

Other Recorded Cases

I have only been able to discover three detailed descriptions of similar stomachs, two being post-mortem specimens in which no accurate clinical observations had been made. The first was reported in 1888 by Menetrier.[2] A painter, aged 38, who had drunk in excess and had had two attacks of lead colic, had complained of anorexia, nausea and diarrhœa for two months, when his legs and abdomen became œdematous and ascites

developed. He rapidly became weaker from the persistent diarrhœa, and died five months after his admission to the hospital. At the autopsy the cause of the ascites was found to be severe perihepatitis, though the liver itself was healthy.

FIG. 6.

Gastritis polyposa (Meulengracht).

The mucous membrane of the stomach from 3 cm. from the cardia to 8 cm. from the pylorus showed a condition of hypertrophy with papillomatous formation, which appears from the description to have been identical with that found in our case. Microscopical examination revealed a universal hypertrophy of the

glands, which were five or six times their normal length, and a less exaggerated development of the submucous coat. The muscularis mucosæ was intact. A similar, but much less marked, hypertrophy was found in the small intestine and to a still less extent in the colon, but there was no development of papillomata; the lymphoid tissue was not increased. Menetrier described a second case, in which malignant degeneration had occurred at one point in a similar stomach, with secondary deposits in the neighbouring glands and the liver.

The second case was published in 1913 by Meulengracht [1] of

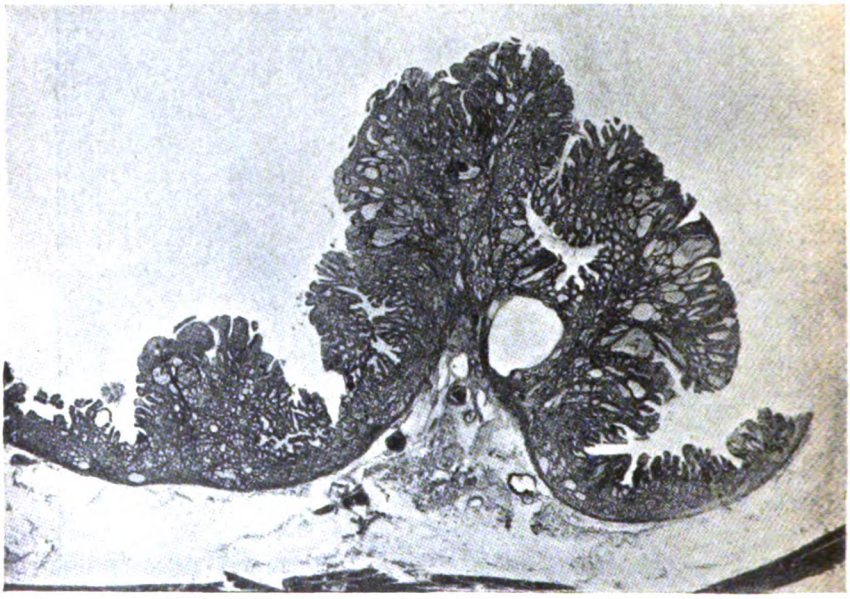

FIG. 7.

Microphotograph of polyp from stomach shown in Fig. 6 (Meulengracht).

Copenhagen under the title of "Gastritis polyposa." The macroscopic and microscopic appearances of the stomach were almost identical with those of the case described above. The stomach had been found during a post-mortem on a woman of 66, who had died in a home for the aged after two years of dementia, during which no abdominal symptoms had been observed. Figs. 6 and 7 are reproduced from his paper.

The third case was published in 1909 by Wegele.[3] A woman, 59 years old, had suffered from diarrhœa for thirty years. More recently pain in the left hypochondrium had developed, with loss of weight and strength. Nothing abnormal was felt in the abdomen. An Ewald test-meal showed complete achylia, and

in the eye of the stomach-tube a blood-stained fragment was found, which on microscopical examination showed an adenomatous condition suggestive of early carcinoma. At the operation numerous gall-stones were removed from the gall-bladder. No tumour was seen or felt on external examination of the stomach, but on opening it the whole mucous membrane was found to be covered with innumerable soft polypi. A gastro-enterostomy was performed. When the case was reported a year and a half later, the patient had lost much weight, and occult blood was present in the stools, but no tumour was palpable. A polypus removed at the operation showed hypertrophied glands with round-celled infiltration of the connective tissue, but no definite malignant degeneration.

A number of other cases of multiple polypi of the stomach, some simple, some undergoing malignant degeneration, have been described, but the three I have summarised are the only ones in which the whole mucous membrane was involved, and in which the polypi, which were non-malignant, appeared to have developed from a condition of generalised hypertrophic gastritis.

REFERENCES

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[2] P. Menetrier: *Arch. de Physiol.*, IV. ser., i. 32, 1888.
[3] C. Wegele: *Mitteil a. d. Grenzgeb. d. Med. u. Chir.*, xix. 53, 1909.

A NOTE ON DENTAL ROOT INFECTION

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THE bacteriological and radiological results in 55 cases of dental root infection are recorded in this note. Circumstances were particularly favourable for co-ordinating these results with those obtained during complete clinical examination of the patients, and it is therefore hoped that this note may have some interest in connection with questions concerning the mechanism and effects of dental, particularly apical, root infection. To this end, the more recent findings in this subject are briefly reviewed and direct comparison with our own series is made.

RECENT INVESTIGATIONS.

It appears that credit must be given to American dental surgeons for first calling attention to apical or "closed" as distinct from "open" dental sepsis. Not before 1915 have we been able to find any definite reference to the subject in British journals. In that year abstracts of two articles, both of American origin, were published in this country, one by Mayo [1] and the other by Gilmer and Moody,[2] describing the closed type of infection and giving in outline an account of the bacteriology. Detailed bacteriological records did not appear until 1923, when Glynn [3] published two articles on the organisms found in periodontal infections and their relations to toxæmia, and in 1924 Broderick [4] recorded a bacteriological investigation in relation to 100 cases of periapical infection. Fraser [5] had also reported in 1923 upon the relation of *Str. viridans* to periapical infection and agreed with Broderick in finding that over 90 per cent. of the infections were predominantly streptococcal. Unfortunately for purposes of comparison, in only the first of these three papers were the streptococci classified according to Holman's method (*vide infra*). But in 1925 Broderick [7] published a further record of 100 cases of apical infection, and on this occasion the fermentative properties of the cocci were investigated in detail, streptococci again being found in over

TABLE I.

Case Series.

No.	Name.	Teeth examined.	Cultural Results.		X-ray type.	Diagnosis.
			Streptococci (Holman).	Brown.		
1	Mr. D.	U. *r.* 1 U. *r.* 3	Both pure strong *Str. salivarius.*	α	A B	No general symptoms.
2	Mrs. B.	L. *r.* 1 L. *l.* 1	Scanty *Str. salivarius.* Sterile.	α —	E Normal	Do.
3	Mr. T.	U. *r.* 1 U. *l.* 1 U. *l.* 2	All sterile.	—	Normal Normal E	Do.
4	Mr. M.-H.	U. *r.* 4 U. *l.* 4	Scanty *Str. salivarius.* Stronger *Str. salivarius.*	α α	E E	Do.
5	Mr. F.	U. *l.* 1 U. *l.* 2 U. *r.* 1	All strong growth *Str. ignavus.*	γ	B B B	Do.
6	Mrs. H.	L. *r.* 6	Strong *Str. fæcalis.*	α	B	Do.
7	Mrs. S.	U. *l.* 4 U. *r.* 4	Both pure strong *Str. mitis.*	α	A B	Do.
8	Mr. S.	L. *r.* 6	Scanty *Str. pyogenes* and *M. catarrhalis.*	β	A	Do.
9	Mr. I.	U. *l.* 2 U. *r.* 2	Mod. growth *Str. fæcalis.*	α	A A	Do.
10	Mrs. F.	L. *r.* 3	Pure *Str. salivarius.*	α	—	Do.
11	Mr. R.	L. *r.* 2	*Str. mitis* and a few *M. catarrhalis.*	α	B	Do.
12	Mr. W.	U. *r.* 4	Scanty *Str. fæcalis.*	α	C	Do.
13	Miss H.	L. *l.* 6	Scanty *Str. salivarius.*	α	B	Do.
14	Mr. W.	L. *l.* 4	Mod. *Str. fæcalis.*	α	B	Arthritis.
15	Mr. M.	U. *l.* 6	*Str. salivarius* + + *M. catarrhalis* + *Diphtheroids* +	α	B	Fibrositis.
16	Miss L.	L. *l.* 7	*Str. ignavus* +	α	A	Spondylose-rhizomélique.
17	Mr. McF.	Alveolar scraping	*Str. salivarius* + +	α	Alveolar rarefaction	Fibrositis.
18	Mrs. E.	L. *r.* 7 Apical abscess	*Str. ignavus* + +	α	B	Rheumatoid Arthritis.
19	Mrs. C.	Alveolar scraping	Scanty *Str. salivarius.*	α	Alveolar rarefaction	Fibrositis and Osteitis.
20	Mrs. H.	U. *r.* 5 U. *r.* 4	*Str. salivarius* + +	α	A B	Fibrositis.
21	Mr. de B.	U. *r.* 2 L. *r.* 3	Both *Staph. aureus* (Hæmol. slight). *Str. salivarius* + +	α	A B	Fibrositis.
22	Mr. B.	U. *l.* 5 U. *r.* 4	*Str. pyogenes* (Hæmol. +). Sterile.	α	B E	Lumbago and Migraine.
23	Dr. W.	L. *r.* 6 L. *l.* 6	Both pure *Str. mitis.*	α	B B	Rheumatoid Arthritis.
24	Mr. C.	U. *l.* 3	Scanty *Str. mitis.*	α	B	Duodenal Ulcer.
25	Dr. B. D.	L. *l.* 8	Scanty *Str. mitis.*	γ	A	Ill results of gastro-enterostomy.
26	Dr. H.	L. *l.* 1	Scanty *Str. salivarius.*	α	E	Jejunal Ulcer.
27	Mr. E.	L. *r.* 2 L. *r.* 1	Strong growth of *Str. salivarius, Staph. albus.*	α	A B	Old gastroenterostomy.
28	Mr. H.	L. *r.* 2	*Str. salivarius* + +	α	B	Gastric Ulcer.

TABLE I (*continued*)

No.	Name.	Teeth examined.	Cultural Results.		X-ray type.	Diagnosis.
			Streptococci (Holman).	Brown.		
29	Mrs. E.	L. *r.* 7	*Str. pyrogenes* (Hæmol. +).	β	E	Septic Anæmia (extreme).
30	Mr. G.	Alveolar scraping	*Str. mitis* +	α	Alveolar rare-faction	Addison's Anæmia.
31	Mr. H.	L. *r.* 3	*Str. pyogenes* + *M. catarrhalis* +	β	B	Addison's Anæmia.
32	Mrs. C. H.	U. *l.* 2	*Str. salivarius* + + *M. catarrhalis* +	α	B	Anæmia. Myelocytic Leukæmia.
33	Mr. H.	L. *l.* 2	Scanty *Str. salivarius.*	α	E	Anæmia.
34	Mr. L.	U. *l.* 2	*Str. pyogenes* + + *Staph. albus* + *M. catarrhalis* +	β	B	Addison's Anæmia.
35	Mr. S.	U. *r.* 6	*Str. salivarius* + +	α	B	Subacute combined degeneration of the Cord + mild Addison's Anæmia.
36	Miss F.	U. *r.* 1	*Str. pyogenes* +	β	B	Septic Anæmia.
37	Mrs. H.	U. *r.* 8	*Str. salivarius* + +	α	B	Septic Anæmia.
38	Mrs. C.	U. *l.* 4	*Str. anginosus.* *M. catarrhalis.*	β	B	Addison's Anæmia.
39	Mrs. B.	Alveolar scraping	*Str. mitis.*	α	Alveolar rare-faction	Addison's Anæmia and subacute combined degeneration of the Cord.
40	Mrs. M.	U. *r.* 7	Scanty *Str. salivarius.*	α	E	Septic Anæmia.
41	Mr. D.	U. *r.* 2	*Str. pyogenes* + *Str. mitis.*	α and β	B	Addison's Anæmia.
42	Mr. B.	U. *l.* 3	*Str. salivarius.*	α	E	Septic Anæmia.
43	Mr. M.	U. *l.* 2	*Str. salivarius* + + *Staph. aureus* (Hæmol. +).	α	—	Addison's Anæmia.
44	Capt. G.	U. *l.* 4	*Str. pyogenes* + + *M. catarrhalis* +	β	B	Addison's Anæmia.
45	Mr. P.	U. *l.* 1	*Str. pyrogenes* + *M. catarrhalis* +	β	B	Addison's Anæmia.
46	Mrs. B.	L. *l.* 4	Strong growth of *Str. pyogenes.*	β	B	Chronic non-suppurative bilateral parotitis.
47	Mr. H.	U. *r.* 5	*Str. salivarius* + + *M. catarrhalis* +	α	B	Gout.
48	Major M.	U. *l.* 2	*Str. fæcalis* + + *Staph. albus* +	γ	B	Angina pectoris and achlorhydria.
49	Dr. S.	L. *l.* 2	*Str. salivarius* + + *M. catarrhalis* +	α	A	Appendicitis.
50	Mr. Y.	L. *l.* 7	*Str. mitis* + + + *Staph. albus* +	α	B	Anorexia Nervosa.
51	Mrs. H.	L. *r.* 5	Scanty *Str. salivarius.*	α	B	Appendicitis and Gastritis.
52	Mrs. H.	U. *l.* 3	*Str. salivarius* + +	α	—	Colitis.
53	Mr. M.	Alveolar scraping	Practically sterile, a few *M. catarrhalis.*	—	Alveolar rare-faction	Subacute combined degeneration of the Cord.
54	Mr. K.	L. *r.* 8	*Str. mitis* + + *Staph. albus* +	α	B	Do.
55	Dr. P.	L. *l.* 4	*Str. salivarius* + +	α	A	Do.

90 per cent. of the cases; he showed that though no specific strain of streptococcus could be held responsible for apical infection, yet the occurrence of the different strains corresponded very closely to their percentage incidence in normal saliva. He suggested therefore that the infection usually occurs from the saliva via the pulp. Still more recently Appleton, Bryant and Zebley [8] presented the bacteriological results of a series of apical cultures and confirm the constant presence of streptococci, but classify them according to their action upon erythrocytes and hæmoglobin, *i.e.* by Brown's method.

On the bacteriological side our own series may be considered as closely parallel to those already mentioned, but the added advantage of the radiological and clinical findings in these cases makes it possible to view them in relation to a few questions of wider interest. In subsequent paragraphs such an analysis is attempted.

Technique Employed

When possible one of the anterior teeth was chosen for examination, so as to provide the best chance of removal without contamination. In every case a radiological examination was made and the appearances classified as indicating one of the types of apical infection to be described later. Teeth surrounded by marked pyorrhœa were avoided, and those included in the series were selected so as to represent as far as possible the type of radiological abnormality predominant in that patient.

The tooth and its surrounding gum were carefully cleansed with alcohol and thoroughly dried. After careful extraction, the tooth was removed from the mouth without touching the mucous membranes, and the forceps, still holding the tooth, handed to the bacteriologist. From the dental roots cultures were made as follows. In those cases in which the affected areas were situated near the apex, rabbit-blood agar plates were gently stroked with the possibly infected area on the root. If the situation was not favourable for this procedure, a very small bacteriological swab or a platinum loop was used to transfer the material from the root to the plate. Before finally spreading the plates, some of the transferred material was also inoculated into tubes of serum-broth. Sub-cultures were made from the plates and broth cultures, and the organisms were identified by the methods referred to later. Incubation was carried out at 37° C.

In order to test the reliability of this method of extraction, the root apices of a number of normal teeth were examined. Besides the three mentioned in the table, six other normal teeth were cultured, and on one occasion only did bacteria develop in our cultures. Considering that the same method has been employed and found satisfactory by the observers already mentioned, it is submitted that reasonably reliable results have been obtained.

Description of Case Series

For simplicity the results of the whole series are given in one table, but, where possible, subdivisions are made according to the main features of the patient's clinical condition. Thus it will be seen that in one section the signs of arthritis and fibrositis are predominant, in another the patients are markedly anæmic, and so on. The classification of the streptococci is given according to both Holman's and Brown's methods. Where spaces have been left, it is to be understood that the particular observation has not been made or that its result is not known. The majority of the records are, however, complete. No contractions have been used except in the case of the radiological results. In these the capital letters inserted are to be interpreted as follows :

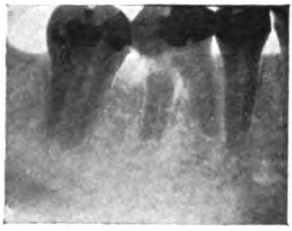
A. At the root apex there is a radiolucent area in the surrounding bone with *regular* outline but ill-defined boundary. The condition is supposed to represent successful localisation of the septic process by tissue reaction.
B. Showing radiolucent area with *irregular* outline but ill-defined boundary. The tissue resistance is here probably breaking down.
C. Showing radiolucent area with a regular outline and sharply defined boundary—probably a cystic condition.
D. Erosion of the bony alveolar margin, often representing residual infection.
E. Thickened periodontal membrane with some pyorrhœa.

Bacteriological Analysis

Before discussing the bacteriological findings it will be best briefly to recall the essential details of the two methods, Holman's [9] and Brown's,[10] of streptococcal classification. Holman's method requires division into two main groups, hæmolytic and

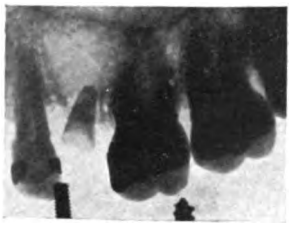
1. Radiological type A (from Case 50).

2. Radiological type A.



3. Radiological type B (from Case 6).

4. Radiological type B (from Case 48).



5. Radiological type C.

6. Radiological type C (from Case 12)

7. Radiological type D (from Case 30).

8. Radiological type E (from Case 2).

non-hæmolytic, and observation of the fermentative powers towards lactose, mannite and salicin. In this way the following chief varieties may be differentiated :

Hæmolytic	*Str. infrequens.*	Non-hæmolytic	*Str. fæcalis.*
	Str. hæmolyticus.		*Str. mitis.*
	Str. pyogenes.		*Str. salivarius.*
	Str. angiosus.		*Str. equinus.*
	Str. equi.		*Str. ignavus.*
	Str. subacidus.		

Brown observes the type of hæmolysis more closely and takes into consideration the production of methæmoglobin. By this method he divides the organisms into the following main groups :

α type.—Immediately around the colony is a zone of methæmoglobinised erythrocytes and a faint outer zone of hæmolysis. (Very weakly hæmolytic or non-hæmolytic.)

β type.—The colony is immediately surrounded by a clear, colourless zone of hæmolysis. (Hæmolytic.)

γ type.—The colony has grown without producing any visible changes in the surrounding medium. (Non-hæmolytic.)

δ type.—The colony is surrounded by a zone of methæmoglobinised cells without any evident disintegration of the erythrocytes. (Non-hæmolytic.)

It is generally considered that when the relationship between these two classifications is studied, *Str. fæculis*, *Str. mitis*, *Str. salivarius*, *Str. equinus and Str. ignavus* belong to the α type, and *Str. pyogenes*, *Str. hæmolyticus*, *Str. infrequens*, *Str. angiosus*, *Str. equi* and *Str. subacidus* belong to the β type. The γ and δ types probably represent short-chained, non-pathogenic saprophytes.

In the present case series, in which the streptococci are classified according to both methods, the above relationship holds good in nearly every case, and it therefore becomes possible to bring together, as Appleton does in his paper, the bacteriological findings of the various observers quoted. This cannot, of course, be done with reference to sub-groups, but the main division into hæmolytic and non-hæmolytic strains is shown in Table II.

TABLE II.

Author.	Number of Dental Cultures.	Alpha and Gamma Streptococci. (Non-hæmolytic.)		Beta Streptococci. (Hæmolytic.)	
		No.	%.	No.	%.
Fraser (1923) . . .	117	114	97	3	3
Broderick (1924) . .	130	121	93	9	7
Broderick (1925) . .	102	93	91	9	9
Appleton (1926) . .	179	169	94	10	6
Present Series (1925–6) .	70	60	86	10	14
Total . . .	598	557	93	41	7

This comparison indicates clearly that purely hæmolytic streptococci must be relatively rare in apical dental infection, and that over 90 per cent. belong to Brown's α type.

It will be seen that in every tooth which from its radiological appearance would be described as infected, a streptococcus has been readily isolated. This is in accord with the findings of each of the authors already quoted and of Fraser [5] (117 cultures), who particularly investigated the point. It is evidently unusual for more than one type of streptococcus to occur, as in the collected series of 598 extractions (see Table II) a double infection is recorded only eleven times. In our own series only one definite double infection was observed. We note, however, that those teeth, the roots of which show radiological indications of very active infection, may give strong growths of other mouth organisms, such as staphylococci and *M. catarrhalis*.

Concerning the origin of the streptococcal infection, it is of interest to note that analysis of our various streptococcal strains according to Holman's method supports Broderick's contention that in the great majority of instances infection occurs from the saliva via the root canal. If the percentage incidence of the various types be recorded graphically, as in Fig. 1, it will be seen that the curve obtained from our record corresponds closely with those representing the figures of Glynn for the salivary incidence of streptococci in normal students, and those of Broderick for apical infection and saliva. This close similarity between the percentage incidence of the various Holman types in saliva and dental root infections certainly appears definitely to support the theory that infection of the teeth usually occurs from the mouth and not from the blood stream.

Many attempts have been made to correlate streptococcal hæmolytic power with virulence, and it appears now generally

to be accepted that, although strong hæmolysis does not necessarily imply high virulence, yet hæmolytic strains, *i.e.* β streptococci, are more likely to be vigorously pathogenic. Organisms of the α type have repeatedly been found in association with chronic and localised inflammatory disorders, and as far as those strains derived from dental septic foci are concerned, their pathogenicity to laboratory animals has been clearly shown by many observers (*vide infra*), and most recently (1925) by Haden [6] in a paper well illustrated by photo- and micro-photographs of the lesions produced. These include vegetations

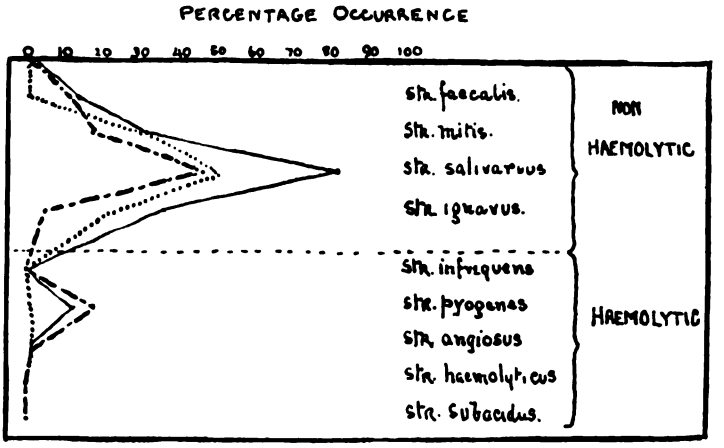


FIG. 1.

Glynn ——; Broderick .....; Present Series —.—.—.—.

on the heart valves, meningitis, eye lesions, nephritis, peptic ulcer and arthritis.

It was unfortunately not possible to test more than seven of the α strains in our series upon animals, but these seven all produced focal lesions. Figs. 2 and 3, reproduced from micro-photographs kindly taken for us by Dr. E. W. Bowell, show examples of foci produced by the streptococci of Cases 18 and 40 respectively, and in them the organisms were easily demonstrated both culturally and microscopically.

The effect upon a rabbit of three weekly intravenous doses of 250 million hæmolytic *Str. pyogenes* from Case 27 is shown in Fig. 4, which is a blood film taken shortly before the animal died eighteen days after the first injection. The hæmoglobin fell from 78 per cent. to 46 per cent. Post-mortem marked focal nephritis was also present.

Probably all α and β strains are to be considered as patho-

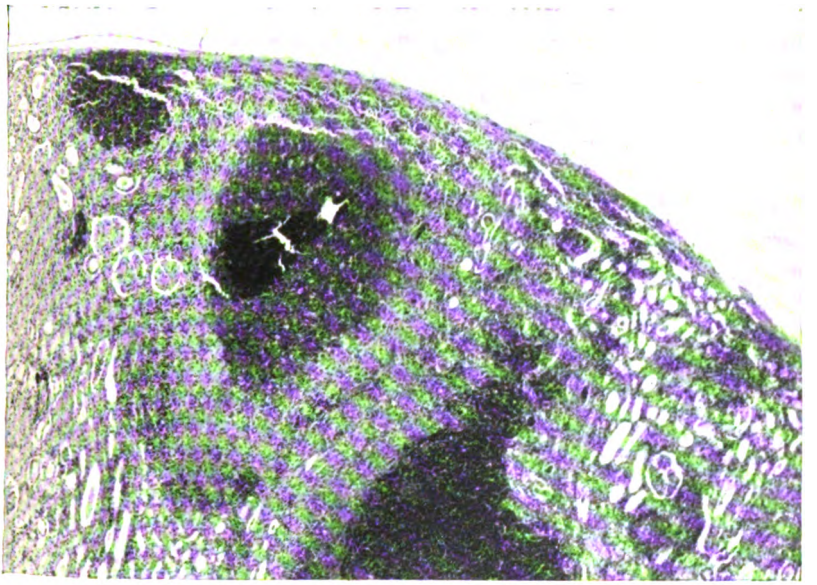


FIG. 2.

Focal nephritis and abscess formation in rabbit following two intravenous doses of 250 million *Str. ignavus* isolated from root apex in case 18.

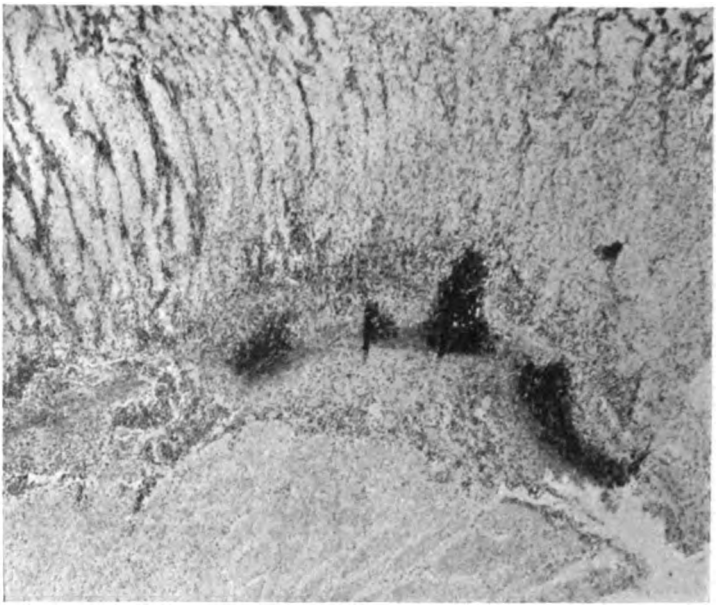


FIG. 3.

Formation of small abscesses in the gastric submucosa of rabbit after intravenous injection of two doses of 250 million *Str. salivarius* from case 40.

genic or potentially so. Four of our γ strains injected into rabbits were apparently without effect on these animals.

Specificity of Bacteria in Systemic Lesions

It is evident that in this series one cannot find any particular streptococcal strain constantly associated with the same type of lesion. Only in the case of anæmia might it be said that hæmolytic strains are relatively common. Seventeen of the patients were definitely anæmic, and in eight of them the apical infection continued a hæmolytic streptococcus and in one a hæmolytic staphylococcus. In two of these cases (Nos. 29

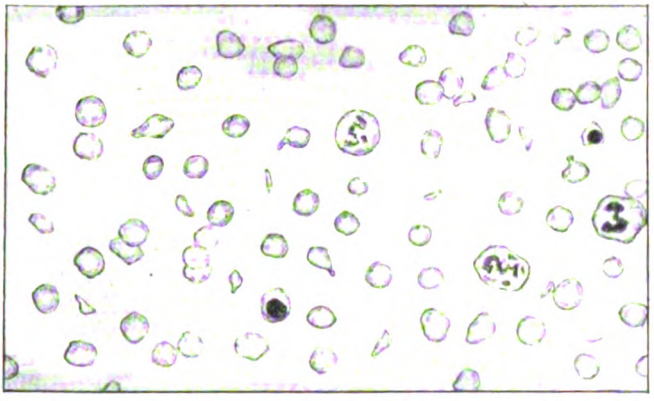


Fig. 4.

Blood film of rabbit injected with *Str. pyogenes* from case 27. HB% = 46.

and 44) the effect of extraction was particularly noteworthy, their hæmoglobin having risen since from approximately 50 per cent. to over 90 per cent. In two non-anæmic cases (Nos. 8 and 22) the streptococci possessed hæmolytic properties and gave the fermentative reactions of *Str. pyogenes*. Also it may here be pointed out that the inclusion in our series of so many cases of anæmia possibly accounts for the slightly higher incidence of hæmolytic strains in our chart of Fig. 1 and in Table II.

Establishment of specific strains of streptococci as causing constant types of lesion in the human subject has, when any of the present systems of classification are adopted, presented serious difficulties. No finality has been reached, and the fact is here clearly illustrated. Taking first those cases representing

conditions of fibrositis and arthritis, it will be seen that, according to Holman's classification, there is no strain in the dental infection which is common to all. It can only be said that in each case the streptococcus belongs to Brown's α type, and it is remarkable that in several cases an organism is present which according to Holman would be termed the common *Str. salivarius* In none of the arthritis cases were vigorously hæmolytic streptococci found in the apical infections.

With our cases of peptic ulceration, the dental streptococci, according to Holman, were just as variable. Here again they belong mainly to the α type, and β streptococci do not appear. It was not possible to find in these cases strains corresponding to the specific organism stated by Girault [11] to occur in 60 per cent. of gastric ulcers, and none of them corresponded in biological reactions to the selective strain described by Rosenow.[12] In fact we again see several marked apical infections with the so-called *Str. salivarius.*

Unfortunately no other clinical condition occurs in our series sufficiently often to permit of any deductions as to the specificity of the infection, and it may be noted that in the groups other than the anæmias the incidence of the Holman types of streptococci simply shows approximation to that found in average salivas and may merely indicate the original source of infection.

On these grounds the suggestion might be made that the factors which determine the production of lesions in any particular patient are concerned more with the presence of lowered tissue resistance at the points attacked than with the specificity or selectivity of the streptococcal strain ultimately found in them.

Radiological Appearances

With regard to radiology, these cases may be reviewed in relation to the prevalent idea that those patients who exhibit sharply defined areas of bony rarefaction are those who do not develop systematic lesions (Group A), whereas those in whom there is root infection without granulomata, but who show ill-defined areas of bony rarefaction associated with other areas of hypercalcification, are the most liable to incur distant lesions (Group B). That is to say, patients are divided into (*a*) those who are immune to systemic infection and produce protective granulomata, (*b*) those unable to do so and therefore susceptible, and (*c*) those whose defences are inadequate or have broken down.

Though this description may possibly be correct if applied to the course of apical infection when once established, we have been quite unable from analysis of our radiological results in these cases to suggest that the appearances of the plates will give a definite clue as to the probability or actual presence of systemic lesions.

All those teeth radiologically classed as A, B or C are devitalised and represent true apical infections. On the other hand, it will be realised that those of Group E do not, strictly speaking, come under the heading of apical infection. Among them were included those which showed only a thickening of the periodontal membrane at the root apex. It was found in our series that eight out of nine teeth showing this thickening gave positive culture results. The radiogram illustrated in Case 2 shows the difference between the two lower incisors, both of which are affected by pyorrhœa, but in the right only is the membrane thickened.

The results as a whole suggest that for practical purposes all devitalised teeth may be regarded as infected, even when no radiolucent area is apparent in the bone surrounding the root apex, and further, that any devitalised infected tooth, whatever its exact radiological appearance, may be associated with general symptoms. It should be observed that all the devitalised teeth examined have shown either a radiolucent area or at least a break in the continuity of the lamina dura—the compact layer of bone lining the tooth socket. It may be that any devitalised tooth showing this layer completely intact at the root apex may be regarded as sterile.

On the other hand, there is reason to suppose from our results that radiological appearances classified as B are usually associated with stronger and more active bacterial infection. For example, among the seventeen roots which gave a vigorous growth of more than one bacterial strain, thirteen would be placed in the radiological Group B and only four in Group A. But again it must be emphasised that the patient's susceptibility evidently does not run parallel to the degree of infection, a fact which is so often obvious clinically and is emphasised by the equal distribution of the B radiological group through the whole case series.

It would seem that, just as bacteriological examination can show whether a virulent organism is present, so radiology can provide fairly reliable evidence as to the extent of the closed septic focus. In fact, our impression after making this series of combined examinations is that radiology alone would always tend to under-estimate the degree of root infection. But the

fact remains that from neither of these investigations is it possible to predict the liability of the patient to generalised effects from the dental foci.

Some Clinical Considerations

It may, however, again be emphasised that when radiology showed only a definitely thickened periodontal membrane (type E) it was possible to obtain a strong growth of streptococci from the root in seven out of nine cases, and that, as already mentioned, it seems to be established that, with more marked radiological changes, infection can be proved in 100 per cent. of the cases.

These facts may be considered in relation to the question of wholesale tooth extraction. That extraction does not invariably remove the infection has been pointed out by Eyre [13] and others, and the residual bone infection which may occur is illustrated by obtaining in this series four positive cultures out of five examples of this condition, Cases 17, 19, 30 and 39 giving x-ray appearances which suggested and cultures which confirmed the presence of organisms. Also it must be remembered that though the changes in the periodontal membrane and the rarefaction of bone can presumably be formed by various types of reaction and various types of mass forming at the root apex, yet our findings suggest that they are all associated with some degree of streptococcal infection. But we feel that there is still no evidence upon which to decide the types of reaction most likely to be associated with systemic involvement, and in which types extraction is therefore most urgently called for. It is a point of importance, however, that radiology apparently tends to under- rather than over-estimate the intensity of the actual apical infection.

Another matter to which this series may call attention is the unsatisfactory naming of various undoubtedly pathogenic strains of streptococci, e.g. *Str. salivarius*, so that clinicians are liable to infer from the wording of a bacteriological report that the organisms isolated are of no importance. Examination of the distribution of the strains in Table I suggests that types such as *Str. mitis* and *Str. ignavus* can be associated with systemic lesions, and the literature contains many direct experimental records proving that such members of Holman's groups are not necessarily harmless. For example, Glynn and Digby [14] report isolation of *Str. salivarius* in cases of lung abscess and puerperal septicæmia, of *Str. mitis* from the vegetations of endocarditis and of *Str. equinus* from lung juice in lobar pneu-

monia and in empyemata. Andrewes and Horder [15] consider that *Str. salivarius* plays no unimportant part in human pathology and recorded it as pathogenic in twenty-six cases, but find that *Str. mitis* and *Str. equinus* are less virulent. Among other similar cases Horder [16] recently described an instance of septic endocarditis with pulmonary infarction caused by *Str. salivarius*. Moreover Glynn [3] and Hartzell and Henrici [17] definitely proved that many of these non-hæmolytic streptococci when injected into rabbits can produce arthritis and focal nephritis, and our few animal experiments with these dental organisms are quite in accord with their findings.

Summary

The constant presence of streptococci in even the earliest cases of apical root infection is demonstrated. From combined radiological and bacteriological findings some evidence is deduced that streptococci are the first invaders coming from the saliva, and that in more advanced cases these are followed by and associated with other organisms common in the mouth.

The frequency with which anæmia is associated with apical infections by hæmolytic streptococci is noted.

No evidence could be obtained that any specific strain of streptococci according to Holman's classification was associated with cases of arthritis or peptic ulceration. It can only be said that in these cases the organisms all belonged to Brown's α type, which is usually considered to denote low-grade pathogenicity.

The same organisms were obtained from a number of symptomless patients, in whom the dental radiological appearances were just as strongly indicative of extensive apical infection. The importance of the patient's local tissue resistance in determining the presence or absence of systemic lesions is thus illustrated.

In all cases the radiological appearances tended to underestimate the intensity of apical root infection, but no particular appearances could be associated with infection by the different strains.

In conclusion we wish to thank Dr. A. F. Hurst for his permission to publish details of those cases which were examined at New Lodge Clinic, and for his kindness in confirming the clinical diagnoses. We are also indebted for several of the radiographs to Dr. P. J. Briggs.

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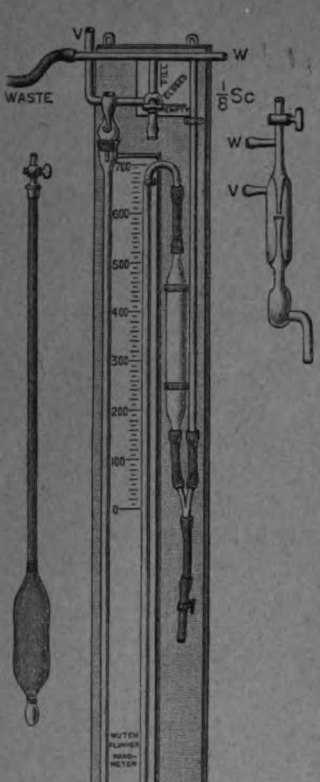

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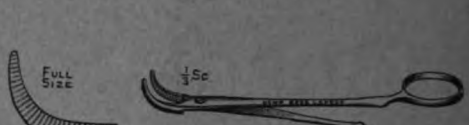

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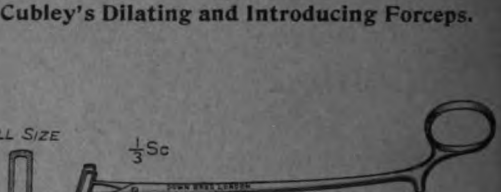

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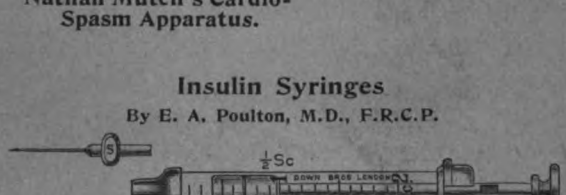

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A COMPARATIVE STUDY OF THE DEVELOPMENT AND PHYSIOLOGY OF IDENTICAL TWINS

By G. P. CROWDEN, B.Sc., M.R.C.S., L.R.C.P., Assistant, Institute of Physiology, University College, London.

From the Physiological Laboratory, Guy's Hospital.*

THE question of the relative importance of the two factors, heredity and environment, in the development of the individual is one of great interest to the biologist, and has given rise to a great deal of controversy. The study of twins has a bearing on this question, for "duplicate" or "identical" twins are believed to be of monozygotic origin, derived from a single fertilised ovum.

This investigation may be described as a human experiment of twenty-five years' duration: an experiment in which two individuals with identical heredity have been subjected as far as seems humanly possible to identical environments. Many independent observers have unwittingly contributed to this experiment, for they have recorded a large number of facts about these individuals and their environment. It is therefore possible not only to compare them at the age of twenty-five, but to trace their growth and development from birth up to that age.

PERSONAL HISTORY

The identical twin brothers G. and L. were born in India, and, after living there from birth up to the age of eighteen months, were brought to England by their parents, as they were delicate and difficult to rear. During infancy they invariably had the same illnesses, both had weak digestions, both suffered from "child crowing." Up to the age of twenty-five they had had, with one exception, the same illnesses; the exception being that L. once suffered alone from an attack of jaundice. Illnesses started in both, either at the same time or with but a short interval between the times of onset.

Many similar instances of the identical susceptibility to illness on the part of identical twins have been recorded by

* The expenses of this research were defrayed out of a grant from the Royal Society to Professor Pembrey.

Galton,[1] and recently Murray[2] has dealt in detail with the evidence on this subject.

L. appears to have a slightly greater recuperative power than G. Their personal habits, hobbies and inclinations are similar; both are keen athletes and motor cyclists, both show a marked aptitude for mechanical work.

Education.—Their parents arranged for them to be sent to the same schools. While at a public school, they both chose to study engineering and subsequently changed at the same time to law. They were in the Officers Training Corps and in the army together. After the war they were at college together, and are now connected with their father's firm as students of patent law.

School records.—Their father very carefully preserved all their school records and half-term and term reports, and from these have been compiled the tables which show their variations in height, weight and other measurements during the eight years 1906 to 1914, *i.e.* between the ages of ten to eighteen years. (Tables III, IV, and Figs. 3, 4.)

From the following quotations from the reports it is evident that the boys developed mentally at approximately the same rates and had identical temperaments. Their masters have been at times at a loss to find synonyms to avoid putting the same remarks on each report.

TABLE I.

EXTRACTS FROM TERM REPORTS.

Michs. term, 1906.—Similar remarks as a whole. Same master (W).
Summer term, 1907.—Both absent for a time, but similar remarks as a whole. Master (S).
Michs. term, 1907.—"Has same failings as his brother." Report by the same master (M).
Lent term, 1908.—"Intelligent, attentive with occasional lapses." Same remark for each by same master (M).
Mid term, 1908.—"Intelligent but most inattentive." Same remarks for each by same master (M). This report shows evidence of confusion between the marks of each.
Michs. term, 1908.—"Shares his brother's fault of restlessness in school." Report by same master (H).
Lent term, 1909.—Accident to G.
Dec., 1911.—Gym. exam.: same marks from instructor.
Michs. term, 1911.—Similar remarks by master (F).
Lent term, 1912.—Similar remarks by master (P. S.).
Mid term, 1912.—Drawing: "Poor clumsy lines"; "Poor lines, too thick." Master (P. S.).
Michs. term, 1912.—"Untidy"; "Very untidy." "Think he and his brother should do homework quite independently." Master (L).
Lent term, 1913.—"Much improved." Same remarks for each. Master (L).
Mid term, 1913.—"Poor style"; "Style poor." "Not as attentive as he should be"; "Not nearly as attentive as he should be." Report by Master (L).
Summer term, 1914.—Good report for each. Master (L).

In these quotations alone we find that seven independent witnesses have placed on record at different times during a period of eight years facts which are in favour of identical rates of development, mental and physical, in the two boys.

The following isolated points of evidence tend to confirm this view.

(1) They were accused of cheating in an examination in mathematics because they made the same mistake in the same problem, but their characters were cleared by their form-master, who reported that they were seated at opposite ends of the examination hall.

(2) During one year at school the total marks gained by G. and L. only differed by four.

(3) In mathematics, French, chemistry and physics they were always very close together, either towards the bottom or the top of the form.

(4) In one of the great public examinations, for which they both offered themselves in the same five subjects, their total marks were 776 and 779 respectively.

(5) It is reported that in an examination they were set to draw a map of England from memory. They both started at the same place and finished at the same place.

(6) They appear to have the same line of thought when subjected to the same environment. On one occasion, when they were being subjected to certain tests, one of them threw a piece of silver paper at someone else, and it was noted by the observer that the other twin had a similar piece of paper ready to throw.

Family History

The only other recorded twins in the family are twin aunts on the father's side.

Their father and mother are both fair. The grandmother on their father's side had auburn hair. The grandmother on their mother's side had red hair. The twins themselves have red hair of an identical shade.

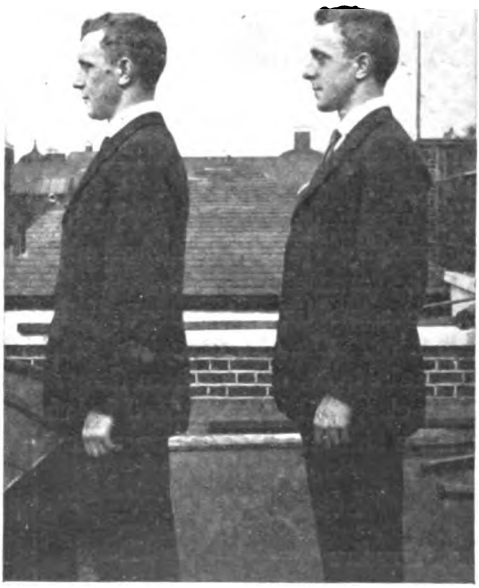
The eyes of G. and L. are an identical shade of blue, exactly the same shade as their mother's, whereas their father's eyes are of a lighter shade.

Reference is made later to the fact that the finger-prints of the twins are also more like those of their mother.

Present State

(a) *Anatomical*

General Appearance.—In stature, physique, profile and front view the twins are at first sight exactly alike. It is only by minute examination and recording the differences that it is possible for the stranger to tell G. from L. As a general rule their striking similarity is emphasised by their wearing identical clothes.



G. Fig. 1. L.
The twins.

Fig. 2.
Composite Portrait made from Fig. 1 by Mr. G. Walker.

Profile photographs superimpose so exactly that the composite appears in no way different from a normal face (Figs. 1 and 2).

x-Ray photographs of their skulls will superimpose in almost every part. Slight differences are noticeable in the frontal sinuses.

Measurements.—The measurements of their heads, as shown in Table II, are very similar.

TABLE II.

HEAD MEASUREMENTS.

	G.	L.
Auricular height . .	138 mm.	142 mm.
Greatest diameter . .	194 mm.	201 mm.
Length of face . . .	123 mm.	130 mm.
Circumference of head .	56·4 cm.	57·4 cm.
Breadth of face . . .	129 mm.	130 mm.

Table III shows their height, chest measurements, biceps, forearm and weight.

TABLE III.

BODY MEASUREMENTS.

	G.	L.
Height, 1921 . . .	5 ft. 7¾ ins.	5 ft. 7¾ ins.
Chest 1913 . . .	32 ins.	32 ins.
Chest 1914 . . .	32 ins.	31½ ins.
Biceps, 1921 . . .	12⅞ ins.	13 ins.
Forearm, Rt., 1921 . .	10¾ ins.	11 ins.
Weight, 1921 . . .	63·82 kilos.	64·2 kilos.

Table IV shows an analysis of the records of the measurements of their height, weight, chest, forearm and arm during the eight years they were at a public school. It will be seen that the degree of difference could almost be accounted for by the possible error in taking the various readings. This table

TABLE IV.

ANALYSIS OF MEASUREMENTS.

From School Records for 8 years. Age 10–18 years.

	Number of coincidences.	Number of variations.	Mean difference of variations.
Height .	10	3	¼ in. L. +
Weight .	3	10	11 ozs. G. +
Chest .	4	9	½ in. G. +
Forearm .	3	10	¼ in. L. +
Arm . .	5	9	0 in. $\frac{L.}{G.}$ ± ¼ in.

shows that they have grown and developed at the same rate during the years between the ages of 10 and 18.

Fig. 3 is a chart of their growth and development in respect of their height, weight, and chest measurement. These curves

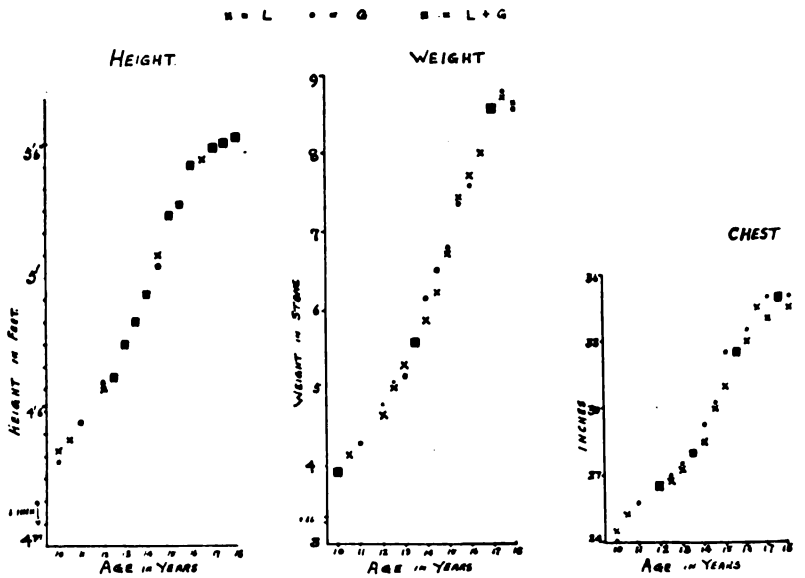


FIG. 3.

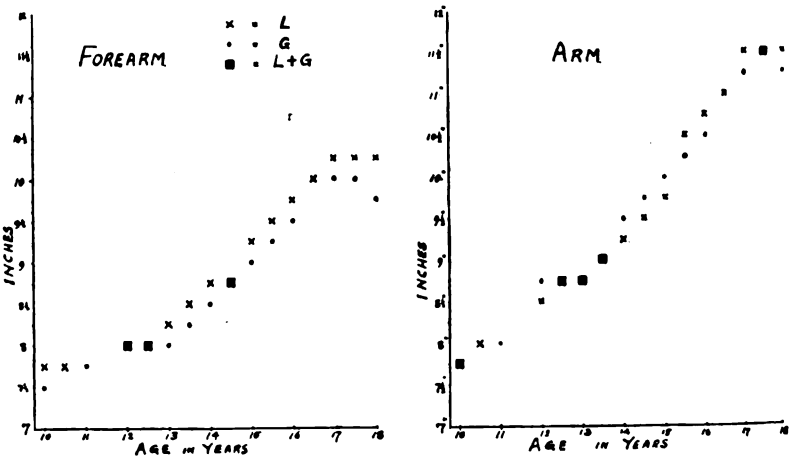


FIG. 4.

and those for their forearms and arms in Fig. 4 show some slight retardation in the early years of their school life which may be associated [1] with the fact that at that time they each had a number of illnesses common in childhood, including measles and whooping cough.

Ectodermal Structures.—The ectoderm, or external germinal layer of the embryo, is believed to be the seat of twinning;[3] it is the place where twinning is initiated and carried out. Hence one would expect to find marked similarity in those structures in the adult, which are derived from a common embryonic tissue, namely the embryonic ectoderm. These structures in the fully developed individual are the hair, eyes, teeth, skin, retina of the eye and the nervous system.

Table V shows that the colour and texture of their hair and the position of the hair whorl on the crowns of their heads are identical. Their eyes are an identical shade of blue. Their teeth show the same abnormality, namely prominence of the left lower canine. Their skins are the same colour and both have a tendency for freckles. Their retinæ, judging from the fact that their fields of vision are practically identical, must be markedly alike. Their nervous systems, judging from the size of their heads, x-ray photographs, and their similarity in ability, both mental and physical, must be structurely very much alike.

TABLE V.

ECTODERMAL STRUCTURES.

	G. L.
Hair . .	Identical shades of red. Curly and of same texture. Whorl commences at same place on top of head.
Eyes . . .	Blue-grey colour.
Teeth . . .	Left lower canine prominent in both.
Skin . . .	Same colour.
Finger-prints .	All loops. Very much alike. G. rm. r. L/3. L. rm. u. L/3.
Palm patterns .	Very similar.

In the examination of the ectodermal structures perhaps the most severe test of their similarity to which they were put was the detailed comparison of the friction ridge patterns on their skins, namely their finger-prints and sole patterns.

Their finger-prints are particularly interesting. Without exception all are loops, and in some cases the number of friction ridges between the delta and the centre of the loop is the same.

From their finger-prints it can be seen that in the case of the right middle finger of each there is almost perfect mirror imaging. In one case the loop turns towards the radius, in

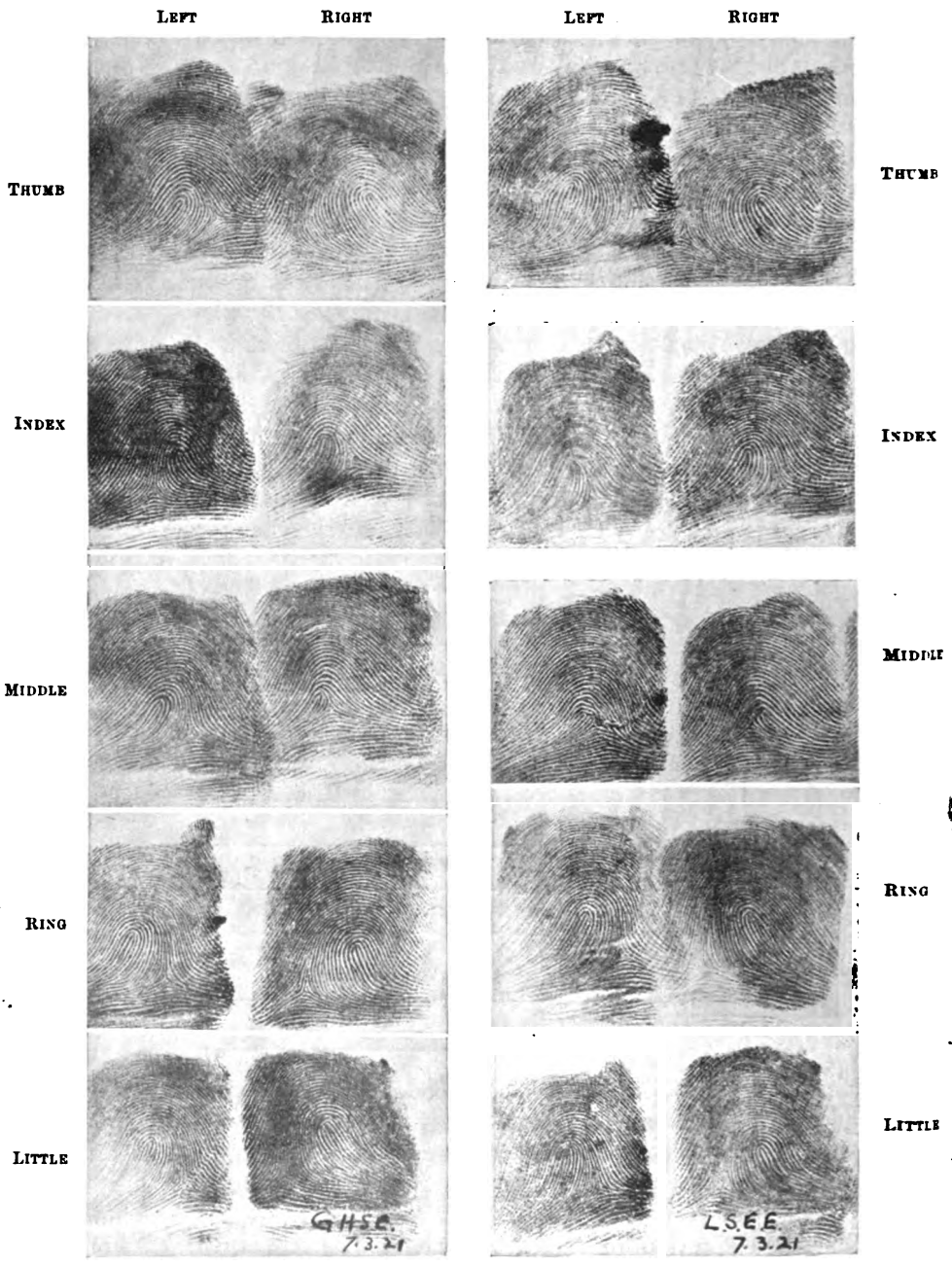


PLATE A

FINGER PRINTS OF G. AND L.

the other towards the ulna, while the number of friction ridges is the same in each, namely 3. Expressed in a conventional manner the friction ridge patterns on the right middle fingers of G. and L. are respectively : r. L_3 and u. L_3.

It is interesting to note that Galton observed that there is an indication that the mother is stronger than the father in transmitting finger-print patterns.[4] Reference Table VI demonstrates that G. and L. have loop patterns on every digit (Plate A). Their mother has loops on nine out of ten digits, whereas their father shows every variety of pattern, namely one arch, three whorls one composite and only five loops.

TABLE VI.

ANALYSIS OF FINGER PRINTS OF TWINS AND THEIR PARENTS.

Fingers.	G.	L.	Father.	Mother.
R. Thumb .	u L_{21}	u L_{23}	W	L
L. Thumb .	u L_{11}	u L_{21}	C	L
R. Index .	r L_8	r L_9	A	L
L. Index .	r L_{10}	u L_7	L	L
R. Middle .	r L_3	u L_3	L	L
L. Middle .	u L_{12}	u L_4	L	L
R. Ring .	u L_{17}	u L_{15}	W	W
L. Ring .	u L_{12}	u L_{14}	W	L
R. Little .	u L_{16}	u L_{12}	L	L
L. Little .	u L_{13}	u L_{12}	L	L

u = ulna. r = radius. L = loop. A = arch. W = whorl. C = composite.

Galton resorted to the friction-ridge patterns on the palm and sole in his studies on the comparison of human identical twins. He held that the "degree of resemblance between duplicate human twins is an index of the strength of heredity as opposed to environment." It is well known that the finger-print pattern is unchangeable throughout life, whatever the environment may be.

The palm patterns of G. and L. are very similar, but we have been unable to get their sole patterns or those of their mother and father.

From consideration of their family history and the above comparison of their ectodermal structures, it would appear that in this case their heredity through their mother is the more powerful determining factor in respect of ectodermal structures. Their finger-prints and eyes are like their mother's. Their hair is like that of their grandmother on their mother's side.

Skeletal Structures.—The similarity in general appearance, stature and profile is but external evidence of the degree of

identity between their bony structures, as made evident by the x-ray photographs of their skulls and hands. The photographs of their skulls and hands can be superimposed so exactly that the resultant picture appears to be that of one only. In the case of the hands the sesamoid bones of the thumbs superimpose. The arm of the father bears a striking resemblance to that of the twin L.

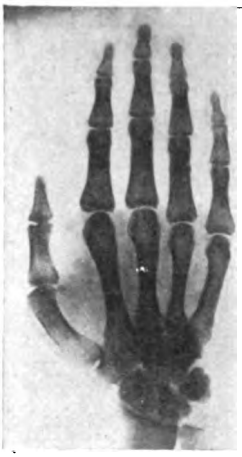


FIG. 5.
Right hand of G.

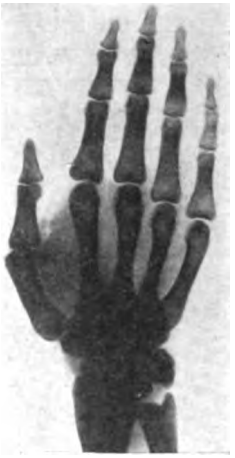


FIG 6.
Right hand of L.

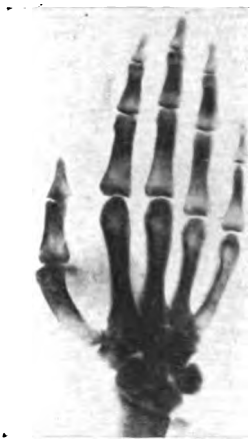


FIG. 7.
Superimposed photograph of right hands of G. and L. taken by Mr. G. Walker.

(b) *Physiological*

Nervous System.—The general similarity in their mental and physical ability, their natural aptitude for mechanical work, and the numerous facts recorded on their school reports as referred to above, all tend to prove that their nervous systems have developed along practically identical lines and at the same rate. Their special senses, as shown in Table VII, are of equal acuteness; their fields of vision show similar variations from the normal. Both are right handed.

TABLE VII.

SPECIAL SENSES.

	G.	L.
Vision . . .	Normal.	Normal.
	Fields of vision show almost identical slight variations from the normal.	
Hearing . . .	Normal.	Normal.
Upper limit of pitch .	17,500 vibrations per sec.	17,500 vibrations per sec.

Cardio-vascular system.—Under this heading the composition of the blood, body temperature and circulation will be dealt with.

Blood.—Samples of their blood were taken and analysed, and their cell counts made by the hæmotologist at Guy's Hospital.

Table VIII shows the results of the examination of their blood. The comment made was that " No difference could be found in hæmoglobin percentage or total counts within the theoretical limits of accuracy of the methods." The grouping test showed that in each case the blood belongs to Group II.

TABLE VIII.

BLOOD.

	G.	L.
Hæmoglobin . . .	80 %	80 %
Red corpuscles . . .	4,800,000 per c.mm.	4,800,000 per c.mm.
White corpuscles . .	8,200	8,200
Group	II.	II.

The differential counts (Table IX) are of interest, because they " show as close an agreement as one could expect to get from the same person on two successive days. Both show the same abnormality (lymphocytosis) to very nearly the same extent." This abnormality is slightly uncommon; it is seen in children and in some pathological conditions. In this case it is probably an hereditary character. It would be interesting to know the differential blood counts of their parents, but up to the present it has not been possible to obtain this information.

TABLE IX.

DIFFERENTIAL BLOOD COUNT.

	G.	L.
Neutrophiles. .	43·2 %	46·0 %
Lymphocytes .	49·2	47·4
Hyalines . .	4·0	4·0
Eosinophiles. .	3·2	2·2
Basophiles . .	0·4	0·4

Temperature.—The temperature of both body and skin are shown in Table X. These readings were taken under identical

conditions and may be interpreted to indicate similarity in their regulation and capillary circulation.

TABLE X.

TEMPERATURE.

		G.	L.
Body . .	Under tongue, 4 p.m.	98·2 °F.	98·4 °F.
Surface. .	Skin of rt. forearm.	89·6 °F.	89·06 °F.
	Rt. cheek.	95 °F.	95 °F.
	Palmar surface tip of rt. Index finger.	81·5 °F.	80·6 °F.

Circulation.—Their resting pulse rates, taken on three different occasions, are shown in Table XI. On the occasion * when the rates were G. 64 and L. 63, their systolic blood pressures were G. 136 mm. Hg. and L. 134 mm., their diastolic pressures were 108 and 104, so that their pulse pressures were 28 and 30 mm. respectively. Their respiration rates on this occasion were G. 19 per minute and L. 20, so that their pulse-respiration ratios were G. 3·3, L. 3·1. Both have normal pulse rates, but on the low side, which is probably accounted for by their athletic training. Their heart sounds and pulse tracings are normal.

Table XI also shows the effect of exercise on their pulse rates. Both did the same amount of work, namely walking

TABLE XI.

PULSE RATES AND BLOOD PRESSURES.

		G.	L.
Normal pulse .	Resting, sitting.	69	69
		*64	63
		63	67
Pulse after exercise	1st 15 seconds.	84	84
	2nd 15 seconds.	76	76
Blood pressure.* .	Systolic.	136 mm.	134
	Diastolic.	108 mm.	104 mm.
	Pulse.	28 mm.	30 mm.

up a step-ladder seven times in a minute. It was found that the pulse rates increased to the same extent in each and dropped to the normal at the same rate after the cessation of the exercise. Their respiration rates showed parallel changes.

Respiratory System.—Their normal resting respiration rates, together with the effects on them of equal amounts of exercise, are shown in Table XII.

TABLE XII.

RESPIRATION RATES.

		G.	L.
Respirations normal.	Resting, sitting.	16 per min.	16 per min.
Respirations after Exercise.	1st 15 secs.	22 „ „	22 „ „
	2nd 15 secs.	20 „ „	20 „ „

Their pulmonary ventilation under identical conditions had the following values: G. 9·5 litres per minute, L. 9·5 litres per minute. Tidal air, G. 0·5, L. 0·55 litres. Vital capacity, G. 4·77, L. 4·5 litres.

Some interesting figures are shown in Table XIII, which gives their "breaking points" under various conditions. In this test each man was given a stop watch, told to take a maximum inspiration and start the watch immediately without looking at it, then to hold his breath for as long as possible and then to stop the watch. The results, G. 85·4 secs. and L. 86·4 secs., when considered in relation to their pulse rates, composition of their blood, pulmonary ventilation and vital capacities, may possibly indicate that their will-power is very similar. L. did hold his breath for one second longer than his brother; he is also capable of slightly greater physical effort.

TABLE XIII.

BREAKING POINT.

		G.	L.
Breaking point.	Normal inspiration.	43 secs.	$42\frac{4}{5}$ secs.
	Normal expiration.	37 secs.	$33\frac{1}{5}$ secs.
	Forced maximum inspiration.	$85\frac{2}{5}$ secs.	$86\frac{2}{5}$ secs.

Muscular Power.—In view of the above-mentioned facts in regard to their anatomical and physiological similarity, it is not surprising to find that they are capable of almost equal physical effort. L. can beat G. by one yard in the 100. Both throw with their right hands. Table XIV shows that they are capable of practically the same static effort in grip and pulling power.

TABLE XIV.

MUSCULAR POWER.

		G.	L.
Grip . . .	Right hand.	53 kilos.	56 kilos.
	Left hand.	41 kilos.	41 kilos.
Pulling power, both arms extended, pulling hands apart.		22 lbs.	22 lbs.
Throwing		Both right-handed.	

It is hoped that the opportunity will arise of investigating and comparing the records of identical twins who from birth, or soon after birth, have been separated and been subjected to different environments.

By a comparison of such an investigation with the results of the one recorded above, some light might be thrown on the relative powers of heredity and environment in determining the anatomical, physiological and psychological development of the individual.

Galton [1] refers to some cases of identical twins separated in early adult life, whose body and mind had continued unaltered up to old age notwithstanding very different conditions of life. He also cites several cases in which "the parents ascribed such dissimilarity as there was, wholly or almost wholly, to some form of illness." In four cases it was scarlet fever.

SUMMARY

In the case which is here placed on record, it appears that, given identical heredity and identical environment for two individuals, A and B, then at any stage in their lives the three following equations (i), (ii), and (iii) seem to be true.

(i) Psychological development of A = that of B.
(ii) Anatomical development of A = that of B.
(iii) Physiological development of A = that of B.

Given different heredity and identical environment equations (ii) and (iii) would not hold, and (i) would probably be untrue in the vast majority of cases.

It remains to be demonstrated, however, how far those equations hold given identical heredity but different environments from birth.

I have been fortunate in meeting another pair of identical twin brothers, who have been together since birth and are now senior medical students. Their physique, temperament and ability tend to confirm the opinion that these three equations hold when both heredity and environment are identical.

Confirmation of this view is also supported by the evidence of Clement Lucas [5] in regard to another pair of twin brothers, who were medical students at Guy's Hospital. The work of Sano on the convolutional pattern of the brains of identical twins is also additional evidence.[6]

Unfortunately it has not been possible to consult the whole of the vast literature on the subject of twins, but as far as I am aware the detailed investigation of a case such as this has not been described previously.

My thanks are due to Professor M. S. Pembrey for very kind advice, criticism and assistance, Dr. Bowel of Guy's Hospital for carrying out the blood examination, Dr. Lindsay Locke for taking the x-ray photographs, Miss Elderton of the Department of Applied Statistics and Eugenics, University College, for help with the analysis of the finger-prints, and Professor Karl Pearson for the loan of apparatus for making certain measurements.

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THE EFFECT OF EXERCISE ON THE RESPIRATORY EXCHANGE IN HEART DISEASE. I.

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DURING the past three years various observations have been made on the effect of exercise on the respiration of patients with heart disease. These investigations have run parallel with others, carried out with Dr. Poulton, on patients in whom the breathlessness was due to chronic bronchitis. The method used has already been described in these papers,[11, 12] but, shortly, the patient breathed into a closed circuit with an attached spirometer, fresh oxygen being admitted automatically as it was required, and the expired carbon dioxide being absorbed. The pulmonary ventilation each minute was read on one dial and the oxygen consumption on another. The normals here used as controls were the same as in those papers.

As the technique has been developed the metabolism has been measured more completely, but in the twenty patients here described only the pulmonary ventilation with the rate and depth of breathing and the oxygen consumption have been recorded. The respiration was taken at rest before exercise and for at least five minutes afterwards.

The exercise consisted of stepping on and off a thirteen-inch block twelve times a minute, and judged by the oxygen consumption to which it gives rise, this is about equivalent to walking at an ordinary rate. In some subjects it was continued for one minute only, and in others for three minutes. This is more satisfactory, as one minute certainly does not allow enough time for equilibrium to be attained.

Very similar observations have been made by Peabody and Sturgis [9] to investigate breathlessness in heart disease. They concluded that the pulmonary ventilation at rest was relatively greater in patients with heart disease; that light exercise produced about the same percentage increase in the ventilation with more subjective dyspnœa; that the ventilation after exercise returned to its resting value more slowly in such patients; and that there was a tendency to more rapid shallow breathing. Our results show general agreement with these, and suggest additions in some particulars.

Clinical Notes of the Cases

Of the twenty patients examined, six (Cases 13–18) had aortic regurgitation as the main lesion, while twelve others (Cases 1–12) had mitral disease, all of these except one (Case 6), who was recovering from a recent attack of rheumatic fever, having signs of mitral stenosis. The two last (Cases 19 and 20) had congenital disease of the heart (morbus cæruleus). It is unfortunate that there should be such a preponderance of men among the aortic group, and of women and children among the mitral group, and allowance must be made for this in drawing any comparisons.

They cannot be regarded as an unselected series, for in most of them the disease was rather severe, except perhaps in Cases 2 and 6. Fourteen were In-patients of Guy's Hospital at the time they were tested, and had been up, getting about the ward, for a few weeks or sometimes less; Cases 2, 5, 11, 12, 13 and 17 were Out-patients when they were tested, but except for Case 13, who had been rather an invalid for ten years, the others had all been in hospital at some time from six months to two years previously.

They were further selected in the sense that they were nearly all rheumatic heart disease, generally without auricular fibrillation; Case 14 was certainly syphilitic, and Cases 19 and 20 were congenital. The other seventeen were probably all rheumatic, though five of them (Cases 1, 9, 10, 15 and 17) gave no clear history of rheumatic fever. Cases of auricular fibrillation were generally excluded, but Cases 3, 11 and 17 had fibrillation, though their pulse had an almost regular rhythm under the influence of digitalis when they were tested.

As regards their after history, seven have not been seen since they were tested, but in only two of these (Cases 3 and 14) was there any reason to expect that their condition was deteriorating much. Six (1, 2, 4, 6, 7 and 13) were much the same one or two years after they were tested, and were able to do light work or go to school. Case 12 had cardiac failure with normal rhythm about six months later. Case 11, who had already had fibrillation, and Case 10, who had not, both had attacks of cardiac failure with auricular fibrillation from one to two years later. Cases 9, 17, 18, and probably 15, died, owing to their heart disease, from one to two years later. Except for Case 18, they did not die in hospital, so details are not known. Notes of each case are given in the Appendix at the end.

Breathing at Rest

With one exception the range for the pulmonary ventilation of our twelve normals was from 6·5 to 9·0 litres a minute. Five of our patients with heart disease had a smaller ventilation than this, but four of these were children, and the fifth a woman who was much lighter than the normals. On the other hand, nine of the twenty patients had a ventilation greater than this, their lighter weight making the difference even more significant.

It is fairer to compare ventilation per sq. metre of surface area, as the metabolism has been shown to vary with this. Du Bois' method [8] of estimating surface could not be used, as the height was not recorded, but using a modified formula of Meeh,[1] $S = 0{\cdot}11\ W^{\frac{2}{3}}$, the comparison is striking. In the normals the average was 4·2 litres per sq. metre, with a range from 3·3 to 4·7 (omitting one result). Only five patients fell within this range, and three of these were well enough to be Out-patients at the time; seven (including the other three Out-patients) were from 20–50 per cent. above the average; and eight had even higher values than this. The findings and the calculated surface area for each patient are given in Table IV at the end.

It is quite clear that in patients with heart disease the ventilation at rest was frequently increased, and that in those who were ill enough to be in hospital for their hearts the increase might be considerable. In the patients with aortic disease the increase was greater than in those with mitral disease, but this may have been partly because as a group they were more seriously ill.

Comparing the rate and depth of breathing, in nine it was faster than any of these normal controls, while in eleven it was within the same range. There was no significant difference between the mitral and aortic groups, though the former were breathing a little more rapidly.

In the patients with mitral disease the breathing was more shallow than normal, half being below the usual range; while in the patients with aortic disease it was deeper than normal, being above the usual range in all except one who had also mitral stenosis. Taking the extremes, the depth was more than 650 c.c. in four—three with aortic and one with congenital heart disease—and 350 c.c. or less in five, all of whom had mitral stenosis. The average results are shown in Table I, with those obtained on patients with bronchitis [11] for comparison; the detailed figures are given in Table IV at the end. The average depth and the range in the patients with mitral

stenosis is almost exactly the same as in the patients with chronic bronchitis, though the rate is rather less.

TABLE I.

BREATHING AT REST.

Subjects.	Surface area (sq. m.).	Pulmonary ventilation.				Rate.		Depth (c.c.).	
		Litres.		Litres per sq. metre surface.					
		Av.	Usual range.	Av.	Usual range.	Av.	Usual range.	Av.	Usual range.
Normals (12) .	1·84	7·8*	6·5– 9·0	4·2	3·3–4·7	15	12–18	520	370–580
Patients with mitral disease (12) . .	1·34	7·2	5·1– 9·5	5·5	3·9–7·7	19	16–25	380	310–520
Patients with aortic disease (6) . .	1·60	12·0	8·3–13·5	7·4	5·7–7·7	18·5	14–23	640	500–750
Patients with chronic bronchitis (6) .	1·93	8·9	7·1–10·2	4·5	—	23	17–28	385	300–530

* In this table and throughout the paper all gas volumes are given as they were measured at room temperature (generally 15–17° C.), saturated with vapour at the prevailing barometric pressure. This was thought accurate enough, as the paper deals mainly with the comparison of average figures.

Although this actual increase in the resting ventilation is considerable, it would not be sufficient to produce subjective dyspnœa normally, but where the capacity for increasing the breathing is restricted, it would be one important factor helping to explain the breathlessness.

VENTILATION DURING AND AFTER EXERCISE

The point which may be taken first, because it was the same in the patients of both groups, is the delay after exercise in the return of the ventilation to its value at rest. Although the absolute figures were so different in the mitral and aortic groups, the shapes of the curves were much the same. When the exercise was continued for one minute only, the ventilation was higher in the first minute after stopping than during the exercise itself in both groups of cardiac patients, although in the normals it had fallen more than 25 per cent. In the normals the ventilation had nearly returned to its value at rest in the third minute, but in the cardiac patients it was considerably above (23 per cent.) in the fifth minute.

When the exercise was continued for three minutes both groups had increased their ventilation sufficiently for their needs, so that a fall could occur as soon as the exercise was

stopped. The fall in the first minute averaged 26 per cent. in the normals, but only 10 per cent. in the cardiac patients. In the fifth minute the increase above the value at rest was less than 5 per cent. in the normals, but still 25 per cent. in the patients. These results are rather similar to what was found in patients with chronic bronchitis.[11] They are shown fully in Tables V and VI, and graphically in Fig. 1, where the ventilation is expressed as so many litres above the value at rest.

Peabody and Sturgis suggested that the ventilation during

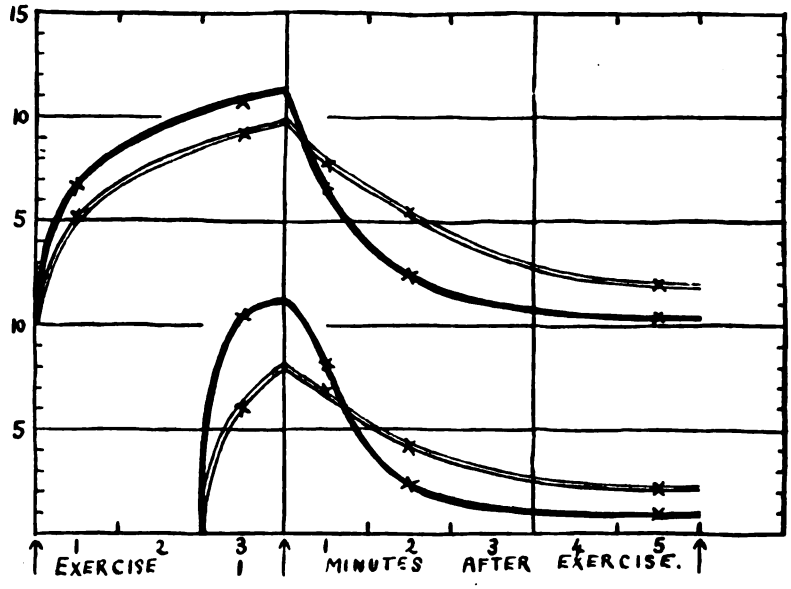

FIG. 1.

Ventilation during and after Exercise in Normals and in Patients with Heart Disease.

The exercise was 12 steps a minute. The upper curves represent the result when the exercise was continued for three minutes; the lower, when continued for one minute only. The thick lines represent the average normal result; the thin lines the average result in patients with heart disease. The ventilation is expressed as so many litres above the value at rest (to bring the curve to the same base line). The actual figures are given in Tables V and VI at the end.

exercise was increased in the same proportion as in health, but the relative increase is not easy to express accurately because of the very varying ventilation at rest and the different possible methods of comparison. Owing to the high value in the aortic group at rest, their ventilation was a little higher than that of the normals, which was again considerably higher than that of the mitral group. The increase due to the exercise was more in the normals than in either—8·3 litres against 5·0 (mitral) and 5·8 (aortic) in the first minute, but there was little difference in the third minute, especially in the aortic group.

If the increase is taken as a percentage above the resting value, it was again highest in the normals during the first minute, and there was less difference in the third minute, this time especially in the mitral group. It looks as though the extra ventilation was less in heart disease at the beginning of exercise, but became almost normal if the exercise was continued.

The further difficulty is that the size of the patients has not been taken into account in making these comparisons. At rest the ventilation per unit of surface area was greater in both groups of cardiac patients. This was also true during exercise, but it seems that the fairest comparison would be to deduct the value at rest and compare the extra ventilation per kilo. body weight, because in stepping on to a block the work done is proportional to this.

If this is done there was little difference in the first minute when the ventilation in both cardiac groups was a little less, but there was a greater difference in the third minute when the ventilation in the cardiac groups was more.

This suggests three stages: the first when the ventilation is actually less than in health, or at any rate less relative to the requirements, with some consequent retention of products such as carbon dioxide; the second when this increased stimulus produces an adequate ventilation which is, relatively to the size of the subjects, greater than in health; and the third when the ventilation is falling, but not as quickly as in health, because of these retained metabolic products which have to be excreted.

Rate and Depth of Breathing during and after Exercise

Just the same difference between breathless and healthy was found in the return of the rate and depth of breathing to their values at rest. In those who only did the exercise for one minute the rate even at rest was rather faster than in the normals, especially in the mitral group (*e.g.* 19·5 and 18 instead of 15). The difference was increased during exercise (25 and 21 instead of 17·5), and remained even five minutes after the exercise was finished (23 and 18 instead of 15).

Naturally these differences were also reflected in the depth of breathing. The aortic group breathed more deeply than the normals at rest, and, in spite of the increase of rate, breathed nearly as deeply during the exercise, a little more deeply for the first minute afterwards, and considerably more deeply for the next five minutes. On the other hand, in the mitral group the breathing was more shallow at rest, and the difference was greatly increased during and after exercise, as there was little change of depth owing to the greater increase of rate.

TABLE II.

VENTILATION AND RATE AND DEPTH OF BREATHING BEFORE, DURING AND AFTER EXERCISE.

Group.	Ventilation (litres).			Rate.			Depth (c.c.).		
	Rest.	Exercise.	5th min. after.	Rest.	Exercise.	5th min. after.	Rest.	Exercise.	5th min. after.
	Exercise, twelve steps a minute for one minute.								
Mitral disease (average of 6)	7·3	12·6	9·3	19·5	25	23	375	505	405
Aortic disease (average of 4)	12·8	18·6	15·0	18	21	18	710	890	830
Normal (average of 6)	7·9	18·2	8·9	15	17·5	15	520	1040	590
Chronic bronchitis (average of 4)	9·2	17·6	11·3	25	32	30	370	550	380
	Exercise, twelve steps a minute for three minutes.								
Mitral disease (average of 8)	7·0	15·7	8·7	18	29	21	390	540	415
Aortic disease (average of 2)	9·5	20·8	13·5	17·5	21	18	540	990	750
Normal (average of 5)	8·7	19·4	9·1	16	19	16	540	1020	570
Chronic bronchitis (average of 5)	8·4	27·0	11·9	19	33	22	440	820	540

In those who did the exercise for three minutes the results were similar, but as the only two patients with aortic disease were less seriously ill, their results approached the normal. As before, the rates were 18 and 17·5 instead of 16 at rest; 29 and 21 instead of 19 during exercise; and 21 and 18 instead of 16 five minutes later. There was little difference between the depth of breathing in the normals and in the aortic group, but in the mitral group the breathing was much more shallow. These results are summarised in Table II, and are given more fully in Tables V and VI at the end.

Some objection may be urged against the use of averages here, but a study of the individual results leads to the same conclusions. For the figures at rest this has already been shown. The first minute of exercise may be taken as a time applicable to all these observations, whether the exercise was continued for one or three minutes. Only six subjects were breathing less than 20 times a minute during the first minute of exercise, 18 being the average rate of the normals (see Table IV). Two of these six had aortic regurgitation, one congenital heart disease, one mitral regurgitation only, and two relatively slight mitral

stenosis. That a normal rate of breathing was unusual in serious mitral disease is emphasised further by the after histories. Of these three with mitral disease (Cases 2, 6 and 7), the disability was slight, as shown by little or no change two years later, while of the two with aortic disease, one (Case 17) died with his heart trouble about a year later, and the other (Case 13) is and was almost completely incapacitated.

At the other extreme the breathing was above 25, in only one patient with aortic disease, but in seven of the twelve patients with mitral disease. Naturally it was the same with the depth of breathing, but the contrast was much more striking. In no patient with aortic disease was the depth of breathing less than 840 c.c. In no patient with mitral disease was it above 600, except in the girl with mitral regurgitation (Case 6), in whom it was 680 c.c. Such a sharp contrast would certainly not be found in all groups, *e.g.* if there were more women among the aortic cases and more mixed cases of mitral and aortic disease, but it is certainly very significant.

It is tempting to suggest that the explanation of this lies in the greater tendency of mitral stenosis to produce pulmonary congestion, for it is generally agreed that the reduced vital capacity of heart disease occurs especially in congestive failure (Siebeck [2] and Peabody and Wentworth [5]). Some experimental results of Drinker, Peabody and Blumgart [8] suggest that the congestion reduces the elasticity of the lungs, and so the vital capacity. Congestion might well reduce the vital capacity in mitral disease more than in aortic disease, with a consequent tendency to more rapid shallow breathing. While the published results on vital capacity in heart disease do not lend much support to this difference, some of our results seem to confirm it.

It is unfortunate that the importance of the vital capacity was not realised at the time these patients were examined, so that it was only recorded in some of them more or less as a matter of routine. The findings for ten of these patients are given in Table IV at the end, and the result is also expressed as a percentage of the calculated value, using Myers' tables of vital capacity for varying body weight.[10]

In the three (two with aortic and one with congenital heart disease) whose breathing during exercise was as deep as normal, the vital capacity was between 80 and 91 per cent., surprisingly high values when their incapacity is taken into account. In the seven with mitral disease whose breathing was more shallow than usual, the vital capacity was distinctly lower, from 42 to 73 per cent. The ratio between the depth of breathing during

exercise and the vital capacity was relatively constant compared to the large variation in the actual figures for each separately.

The results are too few to be certain, but they suggest that mitral stenosis reduces the vital capacity and the ability for deep breathing much more than does aortic regurgitation. The resemblances between these patients with mitral stenosis and those with chronic bronchitis are interesting in this connection. We hope to make further observations on these points.

The Oxygen Consumption

As the oxygen consumption at rest under basal conditions was not determined, little need be said about this. In compensated cardiac disease the basal metabolism is normal, while in uncompensated cardiac disease it is increased.[4, 6] Peabody and Sturgis have found that even with compensated heart disease, standing produced about 10 per cent. greater increase in cardiac patients than in normals.[9]

In these patients the resting metabolism was determined sitting at various periods after a meal, and we have only a rough measure of their surface area. Even so, in the majority the metabolism at rest did not vary greatly for 140–160 c.c. per sq. metre of surface area, our control figure being 164 c.c. Probably this was higher because the normals were going about their ordinary work, while the patients were limited in their activity, some very seriously. In five of them the oxygen consumption was considerably above this figure, about 200 c.c. Two of these (Cases 15 and 18) were among the most seriously ill, and two others (Cases 13 and 16) were severely limited in what they could do, while in the fifth the result was rather unexpected.

Here we were more concerned with the extra oxygen consumption as the result of the exercise, and as the work done in stepping varies with the weight of the subject, the results are expressed as c.c. of extra oxygen per kilogram of body weight. (These are given in Table III with some corresponding figures for subjects short of breath from chronic bronchitis.[12]) Both groups of patients used more extra oxygen during exercise, but the difference was not much. It is curious how patients and normals each obtained more of the required oxygen in the first minute when they knew that the exercise was only lasting for one minute—presumably because of their greater ventilation.

After exercise the differences were greater, the oxygen consumption falling very little for the first minute in the cardiac patients, and afterwards dropping more slowly, while in the normals the fall started sooner and was more rapid. This is very like the patients with chronic bronchitis, and is also similar

to what were found with the pulmonary ventilation. It means that the cardiac patients used more oxygen for the same amount of work (19 c.c. instead of 15 c.c. when the exercise was for one minute, and 52 c.c. instead of 38 c.c. when the exercise was for three minutes) and obtained a smaller proportion of the total amount they needed during the exercise itself (41 instead of 52 per cent. when the exercise was for one minute, and 54 instead of 67 per cent. when the exercise was for three minutes).

TABLE III.

EXTRA OXYGEN CONSUMPTION DURING AND AFTER EXERCISE OF TWELVE STEPS A MINUTE.

Subject.	Extra oxygen (c.c. per kilo. body weight).										
	During exercise.			After exercise.					Total during exercise.	Total after exercise.	Grand total.
	1.	2.	3.	1.	2.	3.	4.	5.			
Exercise for one minute.											
Normal	7·7	—	—	4·2	1·5	0·9	0·3	0·1	7·7	7·0	14·7
Cardiac group	8·0	—	—	6·9	2·7	1·1	0·7	—	8·0	11·4	19·4
Bronchitic group	8·4	—	—	7·1	2·1	0·4	0·2	0·3	8·4	10·1	18·5
Exercise for three minutes.											
Normal	5·2	9·1	11·0	7·7	2·2	1·3	0·9	0·5	25·3	12·6	37·9
Cardiac group	5·6	10·6	11·9	10·3	7·1	3·4	1·9	0·9	28·1	23·6	51·7
Bronchitic group	7·3	10·4	12·5	8·6	5·0	2·5	1·0	0·7	30·2	17·8	48·0

Both these changes would tend to increase the breathlessness, but, as was found with the higher ventilation at rest, the difference would not be enough to produce dyspnœa in a normal subject. The cause of their subjective breathlessness lies in their diminished capacity for increasing their ventilation and oxygen consumption rather than in any objective change in the ventilation and oxygen consumption required. It seems best to defer the further discussion of this until the results are available for the carbon dioxide output at the same time.

CONCLUSIONS

In patients with heart disease the pulmonary ventilation at rest was often increased, and this increase was greater in the more breathless. This agrees with Pearce's theory of cardiac

dyspnœa,[7] but in no case was the increase sufficient to account for their breathlessness, *i.e.* to produce it in a normal subject.

TABLE IV.

PULMONARY VENTILATION AND RATE AND DEPTH OF BREATHING AT REST AND DURING THE FIRST MINUTE OF EXERCISE OF TWELVE STEPS A MINUTE.

Subject.	Weight (kilos).	Surface area (sq. m.)	Rest.				Exercise of twelve steps a minute (1st minute).			Vital capacity.	
			Pulmonary ventilation.		Rate.	Depth (c.c.).	Pulmonary ventilation.	Rate.	Depth (c.c.).	C.c.	Percentage of calculated value (10).
			Total.	Per sq. metre surface.							
1	67·0	1·82	7·3	4·2	20	390	13·4	28	480	1800	42
2	43·0	1·35	5·3	3·9	14	360	8·7	15	580	—	—
3	45·0	1·40	8·2	5·8	24	340	15·3	30	510	1200	45
4	27·0	0·99	7·4	7·5	21	350	13·5	45	300	—	—
5	39·5	1·28	5·3	4·1	16	330	8·8	21	420	—	—
6	38·0	1·24	9·5	7·7	16	590	10·8	16	680	—	—
7	26·5	0·98	5·8	5·9	12	480	8·3	18	480	1800	72
8	53·5	1·56	6·6	4·2	18	360	13·5	30	450	—	—
9	48·0	1·46	10·2	7·0	25	410	13·8	28	490	1600	58
10	56·5	1·62	9·4	5·8	18	520	13·5	27	500	2250	72
11	47·5	1·45	5·9	4·1	19	310	10·5	23	455	2000	73
12	23·8	0·92	5·1	5·5	23	220	9·5	35	270	1100	52
Av. .	43·0	1·34	7·2	5·5	19	380	11·6	26	445	—	—
13	57·6	1·64	10·7	6·5	15	710	15·6	16	970	3200	83
14	63·0	1·75	13·5	7·7	21	640	18·7	22	850	—	—
15	57·0	1·63	17·3	10·6	23	750	24·7	28	880	3500	91
16	53·5	1·56	11·3	7·2	17	670	19·4	23	840	—	—
17	48·2	1·46	8·3	5·7	14	585	11·5	13	880	—	—
18	52·0	1·53	10·6	6·9	21	500	23·2	25	930	—	—
Av. .	55·2	1·60	12·0	7·4	19	640	18·8	21	890	—	—
19	51·0	1·51	8·2	5·4	18	460	18·2	21	870	—	—
20	60·5	1·70	12·7	7·5	11	1200	18·6	14	1320	3250	80
Norm.:											
Max.	79·0	2·02	11·2	5·6	22	700	19·4	24	1210	—	—
Av.	68·2	1·84	7·8	4·2	15	520	16·7	18	930	—	—
Min.	54·5	1·66	6·5	3·3	12	370	12·3	15	690	—	—

During light exercise the ventilation was increased roughly in the same proportion as in health; often the change was less at first but continued longer, so that it was greater if the exercise was continued for some minutes. After exercise the ventilation returned to its value at rest more slowly in these patients than in health.

The changes in the oxygen consumption were similar, and the extra oxygen needed was slightly greater in heart disease. A smaller proportion of the total needed was obtained during exercise, so that more had to be obtained afterwards, and the

return was slower. Both these factors, like the increased ventilation at rest, tend towards the production of dyspnœa, but the extent of the change would not be enough to produce dyspnœa in health. These results confirm and extend the conclusions of Peabody and Sturgis.[9]

TABLE V.

PULMONARY VENTILATION AND RATE AND DEPTH OF BREATHING WITH EXERCISE OF TWELVE STEPS FOR ONE MINUTE.

Subject.	Ventilation (litres).					Rate of breathing.				
	Rest.	Exercise.	1st min. after.	2nd min. after.	5th min. after.	Rest.	Exercise.	1st min. after.	2nd min. after.	5th min. after.
1	7·3	13·4	12·8	11·0	9·0	20	28	24	22	20
2	5·6	8·7	11·4	8·3	6·2	15	15	20	17	16
3*	8·2	15·4	17·0	13·1	10·3	24	31	35	33	31
7	5·8	8·3	7·4	6·3	5·3	12	18	12	11	10
8	6·9	15·8	15·0	11·0	10·0	18	30	26	21	20.
9* †	10·2	13·9	17·2	17·7	15·0	26	28	35	33	33
Av. mitral .	7·3	12·6	13·5	11·3	9·3	19	25	25	23	23
13*	10·7	15·6	14·9	12·8	13·1	15	16	17	16	17
14	11·4	17·6	15·3	15·0	14·0	19	22	22	22	22
15* †	18·0	25·0	25·4	24·6	20·4	25	28	26	24	25
16* †	11·3	16·0	16·7	15·5	12·8	12	18	12	11	10
Av. aortic .	12·8	18·6	18·9	16·8	15·0	18	21	19	18	18
19*	7·7	18·2	21·6	14·6	11·0	15	21	25	26	24
20	12·7	18·6	19·2	15·8	14·6	11	14	15	14	14
Av. congenital .	10·2	18·4	20·4	15·2	12·8	13	17·5	20	20	19
Av. cardiac .	9·6	15·6	16·5	13·8	11·8	18	22·5	22	21	20
Av. normal .	7·9	18·2	16·1	10·2	8·9	15	17·5	17	16	15

* Average of two or more observations.
† Could only do nine steps.

Different types of valvular disease produced different changes in the respiration. Rapid shallow breathing was specially characteristic of mitral stenosis. This seemed to be associated with the reduced vital capacity which was probably dependent on pulmonary congestion. On the other hand, the breathing was often as deep as normal when aortic regurgitation was the main lesion, and the rate only increased as the breathlessness became more extreme; the vital capacity was sometimes very little reduced. The rapid shallow breathing of congestive failure has been frequently observed, but not, so far as I am aware, this contrast between cases of mitral stenosis and aortic regurgitation.

TABLE VI.

PULMONARY VENTILATION AND RATE AND DEPTH OF BREATHING WITH EXERCISE OF TWELVE STEPS FOR THREE MINUTES.

Subject.	Pulmonary ventilation.						Rate of breathing.					
	Rest.	Exercise (1st min.).	Exercise (3rd min.).	1st min. after.	2nd min. after.	5th min. after.	Rest.	Exercise (1st min.).	Exercise (3rd min.).	1st min. after.	2nd min. after.	5th min. after.
1*	8·0	14·6	21·4	21·0	18·9	13·3	19	31	36	34	30	26
2	4·4	8·7	11·6	16·9	11·4	5·9	13	15	16	18	20	16
4	7·4	13·5	17·4	12·6	10·8	9·3	21	45	47	35	30	29
5	5·3	8·8	12·0	9·6	6·8	6·3	16	21	23	20	17	15
6*	9·5	10·8	14·7	12·5	10·6	9·0	16	16	16	15	14	13
10*	9·5	14·5	20·3	18·6	17·6	11·1	18	27	28	24	24	19
11*	6·0	10·5	13·5	11·4	10·2	7·7	17	23	22	19	18	18
12*	5·1	9·5	14·4	12·8	11·6	6·4	23	35	44	37	35	31
Av. mitral .	7·0	11·4	15·7	14·4	12·4	8·7	18	27	29	25	23	21
17*	8·3	12·5	15·3	15·5	13·9	11·2	14	14	15	16	15	15
18*	10·6	23·2	26·3	20·2	19·0	15·7	21	25	27	26	23	21
Av. aortic .	9·5	17·9	20·8	17·9	16·5	13·5	18	20	21	21	19	18
Av. cardiac .	7·5	12·7	16·7	15·1	13·0	9·4	18	25	27	24	22	20
Av. normal .	8·7	15·4	19·4	14·3	11·1	9·1	16	17	19	17	16	16

* Average of two or more observations.

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APPENDIX OF CASE NOTES

1. *John M.*, aged 34, was admitted for breathlessness and precordial pain. He had scarlet fever as a child and was told he had heart disease when 19. He had no further trouble till he was 29, after which he was frequently in and out of hospital, the only symptom in addition to those mentioned being a cough.

The heart was enlarged half an inch to the left and a slight thrill could be felt at the apex. Systolic and presystolic bruits were present. There had never been any swelling of the feet. The pulse was regular from 90–70. The diagnosis was *mitral stenosis and regurgitation.*

2. *Matilda B.*, aged 15, was admitted to Guy's Hospital with rheumatic fever when 13 years old. On her discharge the heart was not enlarged, but there was a systolic bruit at the apex. She continued under observation as an Out-patient, and two years later the heart was enlarged about half an inch to the left. The systolic bruit had persisted, and sometimes a presystolic was heard as well. The pulse was regular. She continued in this condition when she was tested, generally able to go to school, but short of breath on any exertion. The diagnosis was *mitral regurgitation and slight stenosis.*

3. *Elizabeth K.*, aged 43, was admitted for precordial pain of ten years' duration, more severe during the last two years. She had rheumatic fever when 16 and again when 21. Six months before admission she had a cerebral embolism. There was auricular fibrillation, no clinical evidence of enlargement of the heart, but a slight thrill could be felt at the apex, and there were mid-diastolic and systolic bruits. The pulse was nearly regular between 70 and 80, with digitalis at the time she was tested. The diagnosis was *mitral stenosis and auricular fibrillation.*

4. *Bertram D.*, aged 12, was admitted to Guy's Hospital when 9 years old with rheumatic fever and chorea. The chorea was severe, and he was in hospital for three months. The heart was enlarged, and there was a loud systolic bruit at the apex transmitted to the axilla. The heart returned to its normal size, but the systolic bruit persisted. During the next two years he attended as an Out-patient with slight relapses from time to time, at the end of which he was admitted with another attack of chorea. A year later he was readmitted with rheumatic fever, rheumatic nodules and choreiform movements. The heart was enlarged half an inch to the left; there was a systolic and an occasional presystolic bruit; no thrill was present. The pulse was rapid but regular. He was tested when recovering from this attack. The diagnosis was *mitral regurgitation.* A year later he had also developed *mitral stenosis.*

5. *Frank C.*, aged 14, was admitted for swelling and pain in the joints. He gave a history of rheumatic fever seven years previously, after which his heart was said to be affected. The heart was enlarged one inch to the left and slightly to the right. There was a loud systolic and a faint diastolic bruit in the mitral area. He was rested for three months and then discharged after graduated exercises with a diagnosis of *mitral stenosis and regurgitation.* He was tested two years after this admission, when his condition was much the same.

6. *Louie P.*, aged 13, was admitted for rheumatic fever. A month before she had come home from school shivering, and her joints were swollen and painful the next day. This soon disappeared, but her pulse was 120, and for three days her temperature rose to 100 each evening. The tonsils were enlarged and exuded pus. The heart was enlarged half an inch outside the nipple line. There was a loud systolic bruit transmitted to the axilla. After a month in bed she was allowed up and was given graduated exercises, and it was during this period, just before her discharge, that she was tested. The diagnosis was *mitral regurgitation.* Three years later she was in good health with no evidence of mitral stenosis.

7. *Victor S.*, aged 10, was admitted with one month's history of pain in the joints, cough and shortness of breath. There was no previous history of rheumatic fever. Pyrexia (T. 101–102) continued for about ten days. The heart was enlarged, especially to the right. There was a loud rub and systolic and diastolic bruits in the mitral area. The urine contained albumin, blood and casts. Rheumatic fever, pericarditis and acute nephritis were diagnosed. For a long time there was little improvement, and from time to time he had bouts of pyrexia with fresh crops of rheumatic nodules. His hæmoglobin fell to 45 per cent. However, he slowly improved and was discharged after five months with the heart still enlarged and the same bruits. *Mitral stenosis and regurgitation* were diagnosed. He was examined two years later, and seemed in good health. The heart was still enlarged, but there was only a slight degree of stenosis.

8. *Eunice G.*, aged 35, was admitted for breathlessness and precordial pain on exertion. Rheumatic fever and heart disease were first diagnosed when she was 28, but she remembered rather similar attacks as a girl and had always been delicate and anæmic. For some time before admission these symptoms had been getting worse, and her feet had swollen after taking exercise. The heart was enlarged about half an inch to the left, and a slight thrill was present. There was a presystolic bruit at the apex. The hæmoglobin was 90 per cent. The pulse was regular, between 80 and 60. The diagnosis was *mitral stenosis.*

9. *Emily W.*, aged 19, was admitted to hospital for swelling of the feet and breathlessness. When 8 years old she was told by the school doctor that she had heart disease, but she was apparently quite well till she was 18, when she began to have increasing breathlessness and from time to time hæmoptysis. A month before admission the cough became worse and her legs and abdomen became swollen. The heart was enlarged just to the right of the sternal border and to the left anterior axillary line. A thrill was palpable at the apex, and there were systolic and presystolic bruits. The pulse was regular, 120 to the minute, but soon dropped to 90. The diagnosis was *mitral stenosis and regurgitation.* Her mother wrote to say that she died of heart disease two years later.

10. *Mary U.*, aged 28, was admitted to hospital for breathlessness, dizziness and hæmoptysis. She had growing pains when 12 years old, but no further trouble until she was 26, when she began to have a cough and to feel faint, tired and short of breath. She was in hospital for a month, and again six months later for hæmoptysis, and afterwards attended as an Out-patient. The heart was enlarged, about half an inch on the first, and nearly one and a half inches on the third admission. A thrill was present and a systolic and a long presystolic bruit could be heard at the apex. The pulse was regular, about 100, soon dropping to 60. The diagnosis was *mitral stenosis.* About two years later she developed *auricular fibrillation.*

11. *Laura G.*, aged 22, first had rheumatic fever when 12 years old. She had sore throats from time to time, but was able to work after leaving school till she was 20, when she had another attack. She had hæmoptysis shortly before her admission, at which time her heart was enlarged almost to the anterior axillary line. At the apex there was a systolic and a long diastolic bruit. The heart rate was irregular, about 120. The diagnosis was *auricular fibrillation with mitral stenosis and regurgitation.* She improved with rest and digitalis, and attended regularly as an Out-patient. The apex beat had come in somewhat about six months after her discharge, when these observations were made.

12. *George W.*, aged 12, was twice in hospital with rheumatic fever the year before these observations were made. He was then short of breath on exertion. The heart was enlarged to the right of the sternum and about half an inch to the left. There was a presystolic bruit and a thrill at the apex. The pulse at rest was 100. The diagnosis was *mitral stenosis.* Nine months later he was admitted to hospital with heart failure (crepitations at both bases, enlarged liver and œdema), still with regular rhythm. He improved, but was unable to do much a year later.

13. *Benoni L.*, aged 32, had an attack of rheumatic fever when 12 years old. He was admitted into Guy's Hospital when 22 (1913) with a second attack. He had at that time developed aortic stenosis and regurgitation, but little, if any, mitral stenosis. For the six years before he was examined he had been attending Out-patients fairly regularly, complaining of headaches, attacks of giddiness and shortness of breath. The heart was enlarged about one inch outside the mid clavicular line, there was a systolic thrill and rough murmur in the aortic area, and a diastolic murmur just to the right of the mid line at the level of the third costal cartilage; there was also a very faint systolic murmur in the mitral area. The blood pressure was 150/90. *Aortic stenosis and regurgitation* were diagnosed.

14. *Fred W.*, aged 56, was admitted for pain in the chest and breathlessness. He was quite well until a week before admission, when these two symptoms came on suddenly. He had great difficulty in getting his breath, and the cardiac dulness extended half an inch to the right of the sternal border and one and a half inches outside the nipple line. There was a systolic bruit at the apex and an early diastolic bruit in the aortic area. The pulse was water-hammer in type, the blood pressure being 145/85; the rhythm was regular, 110 on admission, soon dropping to between 70 and 80. There was a strongly positive Wassermann reaction. The diagnosis was *aortic regurgitation.*

15. *John G.*, aged about 40. Unfortunately these notes have been lost. All that is known is that he was very short of breath and was diagnosed *aortic and mitral regurgitation.* Although apyrexial when examined, he later developed a temperature, and it was thought that he had infective endocarditis.

16. *Alfred H.*, aged 38, was admitted for shortness of breath. He had rheumatic fever when 7 and again when 18 years old, and had always since suffered from shortness of breath on any severe exertion, and had to lead an easy life. The heart was much enlarged, to the right one inch outside the border of the sternum, and to the left nearly to the mid axillary line. There was a systolic and diastolic bruit in the aortic area, and a systolic bruit at the apex. The pulse was water-hammer in type and regular in rate, dropping from 90 to 60. The blood pressure was 126/76. The urine contained a trace of albumin. There was no history of syphilis and the Wassermann reaction was negative. The diagnosis was *aortic regurgitation.*

17. *Arthur J.*, aged 21, was admitted to Guy's Hospital with signs of cardiac failure. There had been increasing disability during the previous year. There was no clear history of rheumatic fever. The heart was enlarged to the right, and

to the left almost to the anterior axillary line. There were diastolic and systolic bruits at the apex and in the aortic area. The spleen was palpable. The Wassermann reaction was negative. His condition improved rapidly with rest and digitalis. The diagnosis was *auricular fibrillation, aortic stenosis and regurgitation and mitral stenosis.* He attended Out-patients regularly and was tested about six months after his discharge, when his pulse was almost regular with digitalis and his heart dulness nearer the middle line than on admission. The outstanding lesion was then aortic regurgitation. He died about a year later, but unfortunately the details are not known.

18. *George S.*, aged 51, was admitted for shortness of breath on exertion. He was treated for rheumatism of some sort when he was 25, but remained quite well and able to do hard work till three years before admission. Since then he had been alternately in bed and at work, but rarely able to work for more than two months at a time. He was short of breath when talking, and had a cough with rusty sputum. The heart was enlarged about half an inch to the left. There was a systolic bruit at the apex not transmitted to the axilla, and an early diastolic bruit in the aortic area. The pulse was water-hammer in type, and the rhythm was regular, about 80 beats a minute. The blood pressure was 110/50. There was no history of syphilis and the Wassermann reaction was negative. He improved with rest and was tested just before his discharge from hospital. The diagnosis was *aortic regurgitation.* Fifteen months later he was readmitted with general signs of cardiac failure, and died three days later.

19. *George B.*, aged about 20. Unfortunately these notes have been lost. All that is definitely known is that he had always been blue and short of breath on exertion. I think the diagnosis was *Congenital pulmonary stenosis: incomplete septum ventriculorum.*

20. *Walter P.*, aged 26, was admitted for shortness of breath on exertion. He had been very blue and short of breath as long as he could remember. He was very cyanosed, with extreme clubbing of the fingers and an enlarged spleen. His red cells numbered over 11 million, and his hæmoglobin 145 per cent. The heart was only slightly enlarged by x-ray examination, and there were no bruits. The diagnosis was *incomplete septum ventriculorum and congenital pulmonary stenosis.*

PRELIMINARY OBSERVATIONS ON THE TREATMENT OF NEPHRITIS WITH ŒDEMA BY MEANS OF LARGE DOSES OF ALKALIES

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IT is exactly one hundred years since Richard Bright drew attention in this hospital to the relation between diseases of the kidney and the appearance of albumen in the urine. It is of interest to notice that he also commented on the fact that albuminuria is less marked in alkaline than in acid urines. He does not appear to have studied this aspect of the matter any further.

The benefit to be derived from giving alkalies in nephritis with œdema has, however, long been recognised. Given at first in the form of mild alkaline drinks with the object of "flushing out the kidneys," it has of late become the custom to employ much larger doses as a result of the researches and teaching of Martin Fischer and of his colleagues. Cook and Osman [1] † showed that in every one of a small series of cases of nephritis of all types there was a definite decrease in the plasma bicarbonate, thus confirming in some measure one of Fischer's chief postulates, namely that in all cases of nephritis there is an undue accumulation of acids in the blood. Inasmuch as the method described below is not a direct outcome of Fischer's work, it is not possible here to enter into further details of his theories, but the opportunity is welcomed of acknowledging the priority of his work in this field.

M. Baird, J. B. S. Haldane and their colleagues,[2] by producing an experimental acidosis in themselves, showed that the bicarbonate was replaced almost molecule for molecule in the plasma by the chlorides. As we have already shown that the bicarbonate in nephritis is usually low, and it is well known that the chloride content is generally, though not always, high, it seemed probable that if the bicarbonate could be raised to a normal value by giving appropriate doses

* Part of this research was carried out with the aid of a grant from the Medical Research Council.

† They were unaware at the time that this observation had already been recorded.

of alkali by mouth or in other ways, the chlorides would fall and the œdema would disappear, provided, of course, the kidneys could be induced to function adequately.

Such, in brief, is the theory upon which the following method of treatment is founded, and it will serve as a reasonable working hypothesis. It is not possible in the present communication to enter into further details of the many complex factors which have to be considered in the study of œdema and its relation to nephritis.

Before describing the cases recorded below, I should like to express my indebtedness to my colleague, Dr. W. W. Payne, who has been kind enough to estimate the chlorides in these and other cases. It is not always possible when dealing with young children to obtain repeated samples of venous blood for these investigations. The method used here for the chloride determinations was a modification of that described by Claudius,[3] using whole blood from a finger prick; it has proved to be extremely reliable.

The four cases described below will illustrate the method of treatment used and the type of response obtained.

Case 1

D. B., *æt.* 6 years, admitted to hospital 9.3.25. Previous diseases—measles and whooping cough. Six months previously complained of repeated attacks of abdominal pain and became easily tired. Slight puffiness of the eyes in the mornings was first noted at this time, but nothing more until about three or four weeks before admission, when his feet and legs began to swell. The œdema appeared to have commenced in a very insidious manner, and was not preceded by any history of throat, nose or ear trouble. Early in February, 1925, he had an acute illness, which his mother thinks was pneumonia, after which the œdema rapidly increased, involving arms, legs, face and back, with a considerable amount of ascites. It is impossible to discover from the history whether this illness aggravated a pre-existing nephritis, or whether it was the cause of the condition. On admission, there was marked œdema of the face, arms, legs, penis and scrotum; the abdomen was much enlarged and contained a considerable quantity of free fluid. His weight was 20,180 grammes and he passed 120 c.c. of urine, which became nearly solid on heating. In spite of his condition, he was put on a full diet, which included milk, bread, meat and potatoes, etc. The œdema and especially the ascites rapidly increased, until, on March 12th, he weighed 21,760 grammes and passed 283 c.c. of urine. The following day he was given Sod. Bicarb. grains 40 four times a day, a total of 160 gr. in the day. This was increased on the 16th to 240 gr.

per diem. The weight still increased and the volume of urine passed fell to 45 c.c. At this time his condition was critical and was regarded as hopeless by those who saw him. Potassium citrate was added to the mixture in equal parts with the sodium bicarbonate on the 17th. The abdomen was so distended that the umbilicus became everted. The dose was then increased

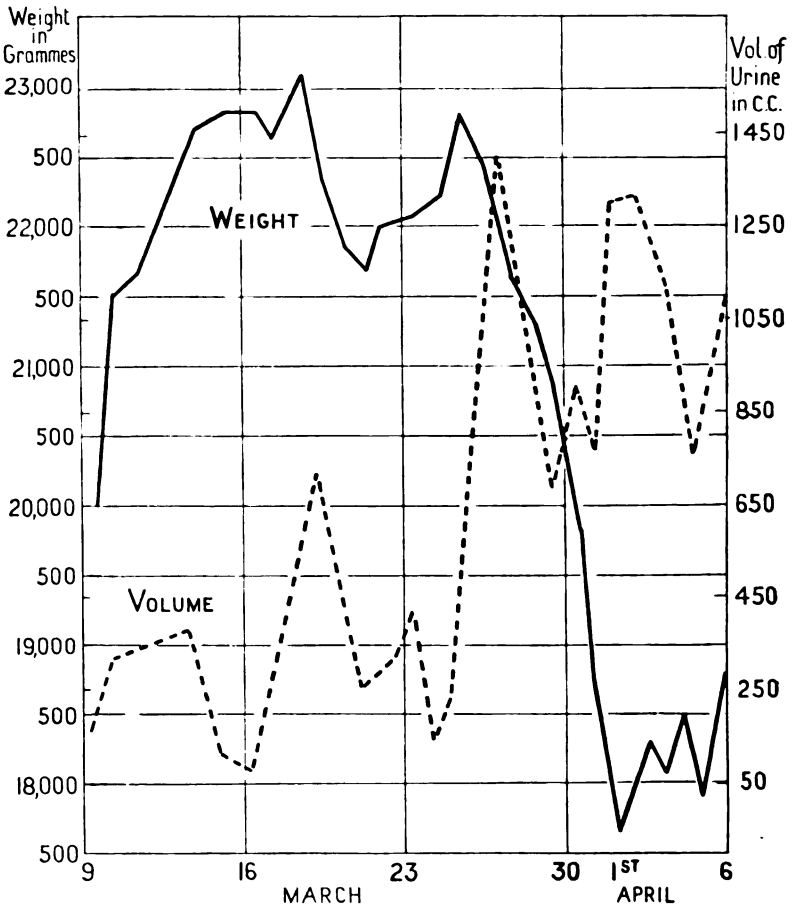

CHART I.

to 960 gr. per diem, given hourly, that is Sod. Bicarb. gr. 20 and Pot. Cit. gr. 20. This produced copious watery stools for three days, after which they became normal. By the 22nd the weight had fallen to 21,940 grammes, or 900 grammes in three days, the volume of urine increasing to 210 c.c. The large doses of potassium appeared to cause some drowsiness, so it was decided to decrease the alkalies again to 240 grains and later 120 grains per diem. As will be seen in the chart, the weight immediately increased to 22,750 grammes and the

volume of urine decreased to 90 c.c. on March 25th. The following day the dose was again raised to 960 grains per diem, and the same result was obtained as before. In the following six days the weight fell to 17,780 grammes and the volume of urine increased to 1,200 c.c., and all traces of œdema and ascites disappeared. For the next three weeks a daily dose of 300 grains was given, and his weight, though showing considerable daily variations, finally settled down at 18,500 grammes, and he thereafter remained normal. During the succeeding five weeks the alkali was gradually withdrawn, and he has since remained free from œdema and albuminuria.

When last seen, September 1926, he appeared to be normal in every way, was attending school and otherwise leading a normal life, with no œdema or albuminuria, not having had any further treatment.

Reference to Table I will show that the maximum result was always obtained when the p_H of the urine was 8 or over. In the present four cases it was found necessary to keep the

TABLE I.

Date.	Total dose of alkalies in grains per 24 hrs.	Weight in grammes.	Vol. urine c.c. per 24 hrs.	Urine p_H.	Albumen pts. per 1,000.	S.G.	Urine chlorides %.	Chlorides whole blood mg. %	Remarks.
9.3.25	—	20,180	120	—	12+++	—	—	—	Full diet. Bed.
10.	—	20,760	270	—	14++	—	—	—	
11.	—	21,450	285	6·4	12++	1045	—	—	
12.	—	21,760	283	6·1	12++	1030	0·544	0·472	Plasma $NaHCO_3$ = 0·031.
13.	—	22,060	300	—	12++	1040	—	—	
14.	160	22,140	180	6·0	9++	1030	—	—	
15.	160	22,670	90	—	—	—	—	—	
16.	160	22,720	45	6·0	14++	1035	—	—	
17.	240	22,670	150	6·0	12	—	—	—	
18.	480	22,850	360	6·1	14	1045	—	—	
19.	960	22,500	630	8·0	1	1040	—	0·396	Profuse diarrhœa.
20.	240	22,050	320	7·4	—	1010	—	—	Diarrhœa.
21.	240	21,950	180	8·0	1	—	—	—	Diarrhœa.
22.	240	22,125	210	7·6	7	—	—	—	
23.	240	22,175	325	8·1	1	1030	—	—	
24.	120	22,250	90	8·0	4·5	1020	—	—	
25.	120	22,750	180	8+	0·5	1025	—	—	
26.	960	22,450	600	,,	0	1040	0·98	0·553	
27.	960	21,740	1320	,,	0	1020	0·50	0·471	
28.	960	21,350	1170	,,	2	1030	0·58	0·470	
29.	960	20,740	600	,,	0·75	1030	—	—	
30.	960	19,840	860	,,	1	1028	—	—	
31.	960	18,950	720	,,	0	—	—	—	
1.4.25	500	17,780	1200	,,	0·75	1015	—	—	
2.	500	17,730	1080	,,	0	1020	—	—	
3.	500	16,770	720	,,	0·75	1024	—	—	
4.	500	16,740	940	,,	2·5	1020	—	—	
5.	500	16,700	1070	,,	0·25	1015	—	—	

urine at a point just alkaline to phenolphthalein ($p_H = 8{\cdot}3$), and for this purpose a drop-bottle of this indicator was always placed near the bed so that each specimen could be tested when passed. Table I also shows the relation between the weight, volume and p_H of the urine, the amount of albumen and the chlorides in both the blood and urine.

Case 2

Ed. K., *æt.* 10/12. Admitted 12.5.25 for generalised œdema and scanty urine. No previous illness. Breast-fed two months, then bottle. Swelling of face gradually increasing and spreading to all parts of the body for fourteen days. Marked ascites. Urine very scanty, large amount of albumen and casts; no blood. Urine very acid. He was put on a milk diet and sugar++ and Pot. Bicarb. and Pot. Cit. equal parts 240 grains per diem by mouth. Table II shows well how the weight fell and the albumen disappeared when the urine became alkaline to phenolphthalein and the blood chlorides reached a normal figure. The alkali was gradually reduced, but unfortunately he was attacked by an infective diarrhœa which was going round the Ward. After a most desperate illness, during which the œdema did not return, probably owing to the diarrhœa, he made a complete recovery. The dose of alkali was still further reduced, and he was eventually discharged œdema- and albumen-free 16.7.25, and has since remained well.

TABLE II.

Date.	Total dose of alkalies in grains per 24 hrs.	Weight in grms.	Vol. urine c.c. per 24 hrs.	Reaction of urine.	Albumen pts. per 1,000.	Urine chlorides %.	Chlorides whole blood mg. %.	Remarks.
12.5.25	—	12,200	Passed into bed.	Acid.	6+	—	—	Fluids. Sugar++.
13.	240	11,980	,,	,,	6	—	0·512	
14.	,,	11,760	,,	Alkaline.	—	—	—	
15.	,,	11,460	90	5·8	6	—	—	
16.	,,	10,770	120	—	6	—	—	Profuse diarrhœa and vomiting.
17.	,,	10,100	—	—	—	—	—	Diarrhœa and vomiting.
18.	,,	10,100	—	—	—	—	—	,, ,, ,,
19.	,,	9,600	—	—	5	—	—	,, ,, ,,
20.	,,	9,600	—	Alkaline to phenolphthalein.	—	—	—	,, ,, ,,
21.	,,	9,350	—	—	0·25	—	—	,,
22.	,,	9,350	—	—	Nil.	—	—	,,
23.	,,	9,350	—	—	1·5	—	—	Less diarrhœa.
24.	,,	9,400	—	—	1	—	—	Bowels normal.
25.	,,	9,650	—	—	Nil.	—	0·450	,, ,,

Case 3

This case was treated on the same lines a year previously and was then discharged œdema- and albumen-free. He will be reported in greater detail elsewhere.

S. B., *æt.* 3 years, re-admitted 4.7.24 for generalised œdema and scanty urine. He had apparently remained well since discharge from hospital 4.9.23, though he did not attend for observation and had had no further treatment. There was marked œdema of the face, arms and legs, and considerable ascites. He was drowsy and passed only 90 c.c. of urine in the 24 hours. The urine was acid and almost solid with albumen

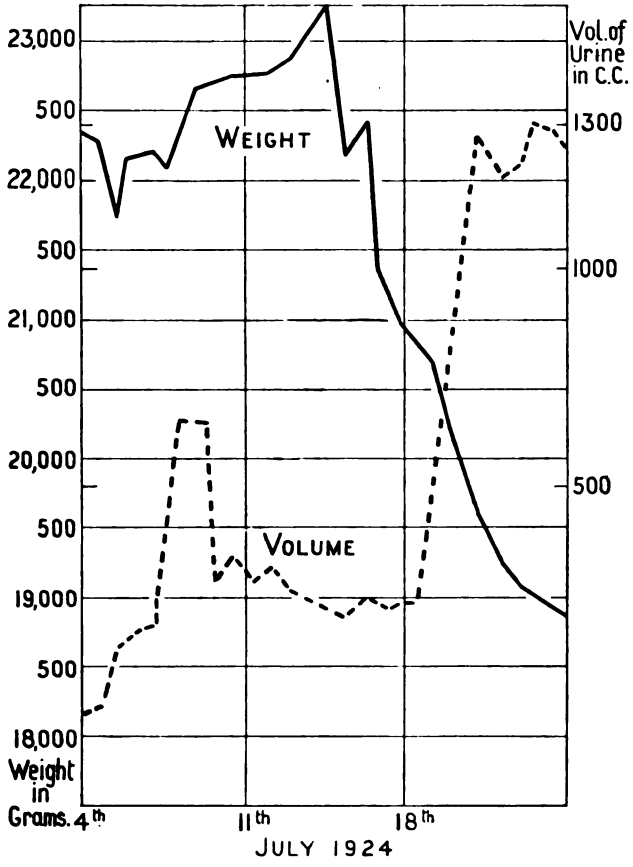

CHART II.

on heating. A milk diet was given and a mixture containing equal parts of Sod. Bicarb. and Pot. Cit. by mouth (for doses, see Table III). Reference to the chart and table annexed will show that, after an initial rise in weight, due mainly to increase in the ascites, as the urine became more and more alkaline the volume passed increased and the amount of albumen decreased. At the same time the weight rapidly fell to normal. He was discharged perfectly well (24.7.24), as the Ward was then closed for an epidemic of whooping-cough. At this time he was having 240 grains of alkali per diem, and he had no œdema or albu-

TABLE III.

Date.	Dose of alkalies in grains per 24 hrs.	Weight in grms.	Vol. urine c.c. per 24 hrs.	Reaction of urine to litmus.	Albumen pts. per 1,000.	Remarks.
4.7.24	120	22,300	90	Acid.	+++	Milk diet. Bed.
5.	480	21,780	240	Alkaline.	+++	
6.	480	22,200	240	Acid.	+++	Farinaceous.
7.	480	22,285	660	Alkaline.	4	
8.	120	22,180	660	,,	4	
9.	480	22,640	360	,,	6·5	Full diet.
10.	480	22,730	420	,,	4	
11.	160	22,780	360	,,	+	
12.	160	23,100	390	,,	+	
13.	120	23,290	360	,,	+	Diarrhœa.
14.	240	22,200	300	,,	+	,,
15.	,,	22,450	240	,,	+	,,
16.	,,	21,550	240	,,	+	,,
17.	,,	21,980	300	,,	+	Bowels normal.
18.	,,	21,300	300	,,	+	
19.	,,	20,700	630	,,	Trace.	
20.	,,	20,150	1,260	,,	Nil.	
21.	,,	19,800	1,200	,,	,,	
22.	,,	19,480	1,280	,,	,,	
23.	,,	19.200	1,300	,,	,,	
24.	,,	19,000	1,280	,,	,,	

minuria. He did not attend for further treatment, and a few weeks later information was received that he had contracted whooping-cough and had died of broncho-pneumonia.

This case was treated empirically before the significance of the bicarbonate-chloride ratio was realised, and therefore no investigations of the blood were made.

Case 4

J. B., *æt.* 14 years. Severe scalds on right arm and back when three years old. During recovery from this, had an attack of hæmaturia, followed by swelling of face and legs. Never been free from œdema since. On admission (4.8.25) weight was 40 kgm., volume of urine 360 c.c., $p_H = 5{\cdot}2$, alb. 14 pts. per 1,000, few r.b.c., many casts. Syst. B.P. 125 mm. Hg. Obvious œdema of face and legs. No ascites. Systolic bruit at apex. Apex beat normal in position. Wass. Reaction, neg. Blood, very lipæmic.

The following table will indicate the course of the case under treatment (see Table on p. 419).

Discharged from Ward

This case is still attending Out-Patients and is having 720 grains per diem. He passes on the average between one and two parts per 1,000 of albumen. He attends school and

TABLE IV.

Date.	Total dose alkalies in grain per 24 hrs.	Vol. urine per 24 hrs.	p_H.	Albumen pts. per 1,000.	$NaHCO_3$ molar conc.	NaCl mg. %.	Urea gms. per 1,000 c.c.	Wt. kgm.	Œdema	Remarks.
4.8.25	0	360 c.c.	5·2	14+	—	—	—	40	++	
6.	—	750 ,,	5·5	8	0·026	0·587	0·39	—	—	B.P. syst. 118 m.m.
7.	240	600 ,,	6	7	—	—	—	40·12	—	
12.	360	1·05 lit.	6	4	—	—	—	41·18	+++	
21.	540	1·95 ,,	7·8	2·5	—	—	0·39	38·59	+	B.P. syst. 118. Blood slightly lipæmic.
28.	870	1·85 ,,	7·8	1·5	—	—	—	39	Nil.	Up for 1 hour.
31.	1080	1·92 ,,	7·9	1	0·0318	0·616	0·36	39	Nil.	B.P. syst. 102. Up all day. Hæmoglobin 64%.
4.9.25	1080	2·58 ,,	8·3	0·5	—	—	—	—	—	
11.	1120	2·55 ,,	8·3	1·5	0·0311	0·596	0·33	39·5	Nil.	
				Dose gradually reduced in spite of albuminuria without return of œdema.						
24.	720	2·4 lit.	7·9	2	—	—	—	39·5	Nil.	

plays games. Any reduction of the dose is attended by slight return of œdema in the legs.

The Method

The details of the method may be summarised as follows.

Alkaline salts are given by mouth (except during coma) until the plasma bicarbonate reaches a normal value, or, more strictly, a figure just above the normal. It will be found that when this point, which may be called "the critical point," is reached, the plasma chlorides, if high, will fall to normal and a marked diuresis will occur, any œdema present subsiding. It is generally possible to give a normal full diet including salt throughout the treatment.

Alkalies are given in the form of potassium citrate, potassium bicarbonate, sodium citrate, sodium bicarbonate, generally in equal parts in water. If sodium bicarbonate alone be used in the dosage necessary to achieve the desired result, it will be found in every case that a stage of initial œdema or increase in existing œdema will be encountered. This initial increase is much less marked if potassium salts be added to the mixture. If potassium salts alone be employed in the required amount, severe diarrhœa may occur, especially in children, and possibly too a toxic action on the heart.

It is certainly safe to increase the dose until the urine becomes alkaline to litmus, though this amount will nearly always be below that required to produce a sufficient diuresis. The effective dose, of course, varies in each case. The lowest up to the present has been 240 grains in the 24 hours, whilst in one case 2,100 grains proved to be ineffectual. The dosage is

distributed evenly throughout the 24 hours, and is increased daily to the optimum.

It is of the utmost importance that large doses of alkalies should not be given in this manner without facilities for investigating the alkali content of the blood at short notice. The most useful single investigation to employ is an estimation of the plasma bicarbonate by the method of van Slyke, Stillman and Cullen (titrating to a constant end-point $p_H = 7{\cdot}4$).[4] In some cases, too, the rate at which the dose is increased must be studied to allow time for a "soaking through" to the tissues without producing a rapid rise in the blood, *e.g.* in the case of a man aged 20 with marked œdema and ascites, the plasma bicarbonate before treatment was 0·0334 (molar), or very slightly below normal. By gradually increasing the dose over a period of 14 days, it was possible to give 950 grains in the 24 hours, the plasma bicarbonate remaining as before.

Dangers of the Treatment

Certain dangers have been encountered in using these large doses, namely tetany, vomiting, and diarrhœa.

Tetany.—The onset of tetany appears to correspond to a plasma bicarbonate of about 0·040 (molar) and over, the actual point varying in different cases. No case of tetany has yet been encountered before the urine had become alkaline to phenolphthalein ($p_H = 8{\cdot}3$ and over), but, for obvious reasons, it would be dangerous to use this value as a guide for the imminence of this complication.

Again, in individual cases, the "critical point" may be (1) below the tetany point (Case 4), (2) at the tetany point, or (3) above the tetany point. In the first group there is, of course, no danger of this complication. In the second and third groups, it is necessary to control the tetany. Experience has shown that this can be most satisfactorily accomplished by giving calcium chloride intramuscularly. It has been found that when using ammonium chloride for this purpose, either by mouth or per rectum, the actual dose to employ cannot be easily assessed, and there is the danger of decreasing the alkali reserve too much, which would lead to anuria, and of course an increase in the œdema. It has been found, too, that such an anuria is even more dangerous and difficult to overcome than tetany. An example will perhaps make this clearer. A girl, aged 22, suffering from chronic parenchymatous nephritis, was œdema-free on 1,100 grains a day. She was up and about the ward and on a full diet, passing about 1 part per 1,000 of albumen in

the day. At this time the plasma bicarbonate was 0·037 (molar) and the plasma chloride 0·536%. Three days later, she contracted a "cold" with a temperature of 99° F. As a result, the bicarbonate fell to 0·033 molar, the chloride being 0·554%, and there was a slight return of œdema. She returned to bed, but remained pyrexial, and, in order to overcome the increasing œdema, the dose was raised to 1,200 grains. At this point she commenced to vomit. As a result of this, she became more alkaline and developed tetany, both the œdema and albumen disappearing. The plasma bicarbonate was at this time 0·0403 molar, the chlorides 0·468% and she was passing large quantities of urine. Calcium chloride, one grain, was given intramuscularly, but as this did not control the tetany, it was decided to give ammonium chloride per rectum. In the course of the next 24 hours, she was given 12 grms. of the latter on each of three occasions, and a further two grains of the former intramuscularly. This dose of ammonium chloride proved to be too large, and as a result a condition of acidosis ensued; with it there was a return of the œdema and albuminuria, the volume of urine decreasing to 6 oz., and she became comatose. The bicarbonate was 0·0235 and the chloride 0·587% at this point. An attempt was made to overcome this acidosis by giving large doses of alkalies per rectum. This proved effective: she became conscious, passed 36 oz. of urine and the œdema began to decrease. Unfortunately she again began to vomit and could no longer retain the alkalies per rectum, again relapsing into coma. Intravenous sodium bicarbonate was tried, but without success. At autopsy broncho-pneumonia was found at both bases.

At the moment, therefore, calcium chloride appears to be the best means of controlling tetany of this type.

Vomiting.—Vomiting, from whatever cause, may be a serious complication in patients already having large doses of alkalies, as they thereby rapidly become more alkaline and quite suddenly pass into tetany.

Diarrhœa.—Diarrhœa is a complication which is found chiefly in children and may be of a very serious nature. It also can largely be controlled by intramuscular injections of calcium chloride.

Results

After the stage of initial increase of œdema, the "critical point" is reached and is accompanied by a marked diuresis, disappearance of œdema, and a decrease in the amount of

albumen passed. This latter is not entirely accounted for by the dilution due to the diuresis. If the alkalies be withdrawn at this stage, the output of urine at once becomes less and the œdema and albuminuria return. If, however, the dosage be maintained at this point for a varying length of time, neither albumen nor œdema reappears, and the reduction of the dose may be gradually effected, and finally the alkalies may be withdrawn. The shortest time in which it has been possible to withdraw the dose entirely after the commencement of treatment is six weeks.

Whilst undergoing a course of treatment as outlined above, each case passes through four stages, the duration of which varies with the severity of the condition, the length of time it has been present, and the rapidity and vigour with which the treatment has been prosecuted. These stages may be conveniently described as :—

(1) The stage of initial swelling.
(2) The stage of subsidence of swelling.
(3) The stage of balancing-up.
(4) The stage of withdrawal of dosage.

For example, in Case 1, Stage I lasted from 9th March to 18th March. As explained above, the dose was then dropped and increased again, the "critical point" occurred on the 25th, which marks the commencement of Stage II. This stage ended on 3rd April. The next Stage, III, extended over three weeks. Stage IV occupied the remaining five weeks.

During the course of a research on the treatment of nephritis, five cases of anuria were encountered. Unfortunately all these cases occurred in young children, who were *in extremis* and from whom it was not possible at the time to obtain blood for chemical examination. In addition several cases of anuria due to other causes have been met with, and in all the plasma bicarbonate was below normal. These cases include pyelo-nephritis, metallic poisoning, and cardiac failure.

The treatment of anuria will be discussed in detail in another paper, when more evidence has been obtained, but it may be of interest to note in connection with the cases described above that the following method of treatment was successfully carried out in all the cases of anuria so far met with.

A mixture containing 10 grains each of Pot. Cit., Pot. Bicarb., Sod. Cit., Sod. Bicarb., is given by mouth (or in cases of coma 3% solution per rectum) at hourly or two-hourly

intervals until the urinary flow commences. At this point, the alkalies are discontinued until it appears that the diuresis is about to diminish. Thereafter alkalies are again given at intervals sufficient to maintain an adequate flow of urine. The dose necessary to achieve this object varies in each case, but it would appear to be quite safe to employ such dosage empirically in these cases, provided it is decreased when the urinary flow is established.

For example, a girl, *æt.* 15½, with pyelo-nephritis and one year's history of slight puffiness of face. Urine contained pus, *B. coli*, casts, albumen, and blood. Slight generalised œdema. Drowsy. Slight twitching of fingers. Anuria 3 days. Blood urea twice normal, $NaHCO_3 = 0{\cdot}026$ (molar conc.), whilst having 200 grains of alkali per diem. Dose increased to 560 grains per diem. Immediate diuresis. Relief of coma. Ultimately discharged from hospital albumen- and œdema-free.

Scarlatinal Nephritis and its Prevention

Through the courtesy of Dr. Woodfield, Superintendent, and of the Medical Officers of the Park Fever Hospital, Hither Green, I have been able to study the prophylactic effect of alkaline therapy upon scarlatinal nephritis. For this purpose two wards of scarlatinal cases were given alkalies from the time of admission until discharge. Three wards of scarlet fever cases not on alkalies were used as a control. During a period of three months 431 cases of scarlet fever were admitted—281 in the control wards and 150 in the "alkaline" wards. All the cases in the latter were given a mixture containing 15 grains each of potassium citrate and sodium bicarbonate three times a day by mouth, or 90 grains in the twenty-four hours. Of the control cases (281), ten developed albuminuria or nephritis (4 per cent.). In the "alkaline" wards of 150 cases only two developed nephritis and no cases had albuminuria without nephritis (1⅓ per cent.). It is to be noted that in both these two cases the 90 grains of alkali were insufficient to turn the early morning specimen of urine alkaline, though the later specimens were alkaline. Furthermore, both these cases were albumen-free in forty-eight hours from the onset of the nephritis. With the prophylactic use of larger doses it seems probable that the liability to nephritis in scarlet fever could be entirely eliminated.

With the co-operation of Dr. C. K. Colwill, working at the Monsall Fever Hospital, Manchester, the following investigation was also carried out. By estimating the *p*H of the early

morning urine in a series of scarlet fever patients throughout the course of the disease, it became apparent that such cases could be divided into two main groups: (A) The Acid; (B) The Alkaline.

The grouping is purely arbitrary. All cases with an initial urinary p_H of 5·0 and under comprised the "acid" group, and all cases with an initial p_H of 5.1 and over the "alkaline" group. In all 109 cases were studied. Of these—

21, or 20 per cent., fall into Group A—the "acid group;
88, or 80 per cent., fall into Group B—the "alkaline" group.

In all cases of both groups, roughly between the tenth and thirtieth days of the disease, the urine becomes more acid, and it is during this period that albuminuria and nephritis are likely to occur. Of the 21 cases in Group A, 14 (or 67 per cent.) developed albuminuria or nephritis. Of the 88 cases in Group B, only 3 (or 3·4 per cent.) developed albuminuria or nephritis. It would appear, therefore, that persons belonging to Group A, on contracting scarlet fever, are extremely liable to develop albuminuria and nephritis, whilst those belonging to Group B are much less liable to these complications.

Further, from the work at Hither Green it would appear that Group A cases, if given alkalies prophylactically, will not develop nephritis, whilst Group B cases do not require prophylactic treatment.

The above figures will serve to show the value of alkalies in the prophylactic treatment of scarlatinal nephritis and albuminuria.

Summary

It is impossible, at the present time, to say how far the method of treatment described above will be of value in the treatment of nephritis with œdema. Many more cases will have to be studied and followed up before the limitations of the method can be defined, but there would appear to be sufficient evidence now that this method of treatment is of real value. It is realised that the procedure here described is only in a crude state, but it is hoped that with further investigation a more effective and safer method will be evolved.

I should like to take this opportunity of expressing my thanks to the physicians of this hospital, who have allowed me to investigate and treat their cases, to those house-physicians who have assisted me in the treatment, and to Prof. Adrian

Stokes and Mr. J. H. Ryffel for their kindly advice and for laboratory facilities.

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THE PLUMMER-VINSON SYNDROME
(SPASM OF THE PHARYNGO-ŒSOPHAGEAL SPHINCTER WITH ANÆMIA AND SPLENOMEGALY)

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

UNDER the title of "Hysterical Dysphagia" Plummer and Vinson of the Mayo Clinic described in 1921 a remarkable syndrome which had not hitherto been recognised. Among 69 cases of functional dysphagia 37 had a "secondary" anæmia, with hæmoglobin varying between 27 and 60 per cent., and 12 splenomegaly. So far as I know, no other cases of the kind have been reported. The following case, which corresponds very clearly with Vinson's description, is therefore worth recording, though the streptococcal glossitis, which was a very prominent symptom, was not described by Plummer and Vinson. In their cases recovery followed the administration of iron and arsenic, encouragement, and the passage of an œsophageal sound, guided by a previously swallowed silk thread, but recurrences sometimes occurred. A condition of hypothyroidism sometimes followed recovery from the dysphagia.

DESCRIPTION OF CASE

Mrs. M., aged 41, was admitted to New Lodge Clinic in April 1926. She became anæmic ten years before after the birth of a child. Two years later she first experienced difficulty in swallowing. Her tonsils were enucleated on account of this, but no improvement followed. Ever since she had felt weak and unwell and her tongue had been sore. During the last year she had been much worse, and dyspnœa had developed. She had also had pain over the heart, radiating down her left arm, on exertion, and for a time complained of "pins and needles" in her hands and feet. The dysphagia had always been intermittent, and was no worse now than it had been eight years ago.

On admission she complained of a painful tongue; its surface was smooth and pale, and covered with a thick coating of mucus. It thus differed from the Hunterian glossitis of Addison's anæmia, in which the tongue is always clean. The spittle contained numerous leucocytes and gave a strong growth of *Streptococcus longus*. Some localised and not severe pyorrhœa alveolaris with slight gingivitis was present. The patient was pale but without any yellow tinge.

The red corpuscles numbered 3,540,000 per cub. mm. with

48 per cent. hæmoglobin, giving a colour index of 0·65. The hæmoglobin percentage had been 65 in January 1925. There was considerable poikilocytosis and slight anisocytosis with some polychromasia and punctate basophilia. No megalocytes were seen, and the average size of the red corpuscles was 6·82 μ compared with the normal of 7·23 μ. No nucleated red cells were found. The leucocytes numbered 5,720 per cub. mm., with 57 per cent. polymorphonuclear cells, 9 large and 32 small lymphocytes per cent., 2 eosinophils, and 1 mast cell per cent. Van den Bergh's test gave completely negative reactions, both direct and indirect. The Wassermann reaction was negative.

The spleen was hard and reached one inch below the left costal margin. The liver was not palpable.

Examination of the nervous system showed no abnormality, except that both ankle-jerks were lost and there was some impairment in the vibration sense over the legs and sacrum but not the arms.

The patient was quite unable to swallow a Ryle's tube, and owing to the spasmodic obstruction at the entrance to the œsophagus it proved impossible to introduce an ordinary stomach tube, so that the gastric secretory functions could not be investigated.

The x-rays showed considerable " hesitation " in the passage of food from the pharynx into the œsophagus; when the food had once entered the latter it passed normally down and into the stomach. In spite of cocainisation and the injection of morphia it was found impossible to pass an œsophagoscope beyond the junction between the pharynx and the œsophagus owing to the tight spasm of the sphincter. It was also found impossible to pass a mercury tube.

The absence of megalocytosis together with the low colour index and the negative van den Bergh test definitely excluded Addison's anæmia, in spite of the glossitis and enlarged spleen. Moreover, the glossitis, though otherwise resembling that of Addison's anæmia, differed in being associated with excessive secretion of mucus. The symptoms, which had at first suggested the possibility of subacute combined degeneration of the cord, were probably due to slight neuritis following the prolonged administration of arsenic.

With treatment of the pyorrhœa, a hydrogen peroxide mouth wash, and the administration of iron she steadily improved. The glossitis became much less severe, and she regained her normal strength; the red corpuscles increased in number in three months to 4,660,000 per cub. mm., and the hæmoglobin percentage rose to 85. The dysphagia became much less marked, though it did not completely disappear.

Commentary

Vinson described the dysphagia as hysterical, and suggested that the prolonged unbalanced diet caused the enlargement of the spleen and secondary anæmia. But there are many other

conditions in which an equally unbalanced diet is taken for months or years, but in which no anæmia and no enlargement of the spleen occurs. For example, the treatment of sprue with a purely milk diet results in the disappearance of the severe anæmia which is often present, and the spleen never becomes enlarged, and formerly, when chronic nephritis was treated for months or years with a milk diet, splenomegaly never developed. Moreover, in the case just described the anæmia appears to have preceded the dysphagia, and the patient also never took a really unbalanced diet, as with great care in chewing her food and eating very slowly she was able to take an ordinary diet, except occasionally for a few days at a time. Lastly, the dysphagia appeared to have much more the character of a reflex spasmodic condition than an hysterical manifestation, the result of suggestion and curable by psychotherapy.

It seems more probable that the dysphagia is due to a reflex spasm caused by local inflammation, due to the same streptococcal infection which led in this case to the glossitis. The anæmia and splenomegaly would then be due to the streptococcal infection. This would explain the improvement in all symptoms following treatment of the oral sepsis.

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AN UNUSUAL COMPLICATION OF A PERSISTENT MECKEL'S DIVERTICULUM

By NILS L. ECKHOFF, Surgical Registrar, Guy's Hospital.

THE following case is published on account of its extreme rarity; I have been unable to find any record of a similar condition being observed at this hospital.

A. H., a boy of 8, was admitted to Job Ward under Mr. Philip Turner for acute abdominal pain.

Apart from measles the boy had previously suffered from no disease, but on two or three occasions he had complained of dragging pains about the umbilicus, which had passed off completely, without any more serious symptoms developing.

Two days before admission he developed a sudden severe attack of central abdominal pain, made much worse by walking or moving about. Later in the day he vomited once. His bowels had been opened as usual on the morning of the onset of the pain, yet an aperient was administered by his mother. This acted freely, but increased rather than diminished the pain. The following day the pain was no better, being more marked on the right side of the abdomen. The bowels were opened satisfactorily, and no vomiting occurred. On the third day he was admitted to hospital.

The boy was healthy-looking, with a good colour, but was obviously in great pain. His temperature was 100·8° and his pulse rate was 108. His tongue was dry and furred, and his skin dry.

On examination of the abdomen it was seen to move only a little with respiration. There was general abdominal rigidity, more marked on the right than the left, just below the umbilicus. Here also the tenderness was at its maximum, and palpation was resented. The urine was normal.

A diagnosis was made of general peritonitis, probably due to an acute appendicitis.

The abdomen was entered by an incision at the outer margin of the right rectus. On incising the peritoneum some sero-pus at once escaped, establishing the diagnosis of peritonitis. A gauze roll was packed lightly into the abdomen, displacing the small intestine to the left. The cæcum was delivered, and with it, the appendix, which was very red, but there was no sign of gangrene or perforation, and the peritoneal injection was no greater than that of the surrounding small intestine.

The appendix was, however, quickly removed in the usual way.

The gauze roll was now removed, and an attempt made to remove the excess of peritoneal exudate, in order to examine the abdomen more fully. In attempting to pass a sponge towards the left iliac fossa, some obstruction was met with. This was soon shown to be due to something running from the lower ileum to the umbilicus. The ileal end of this structure had the appearance of a Meckel's diverticulum, but, again, it showed no more evidence of inflammation than the surrounding gut.

As it was traced towards the surface, a marked constriction was noticed, about 1½ inches from its ileal attachment. Beyond

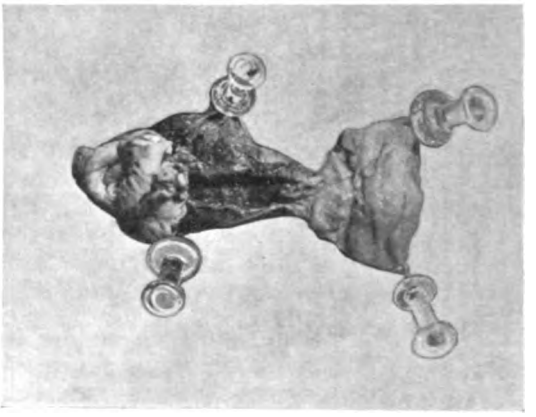

FIG. 1.

Meckel's diverticulum, removed by operation, showing severe inflammation of distal half, between a central hour-glass constriction and the umbilicus.

this it widened out towards the umbilicus, and, although the umbilical end could not be inspected properly through the existing incision, it seemed to be markedly injected.

Accordingly the ileal end of the diverticulum was cut through, between clamps, and the stump closed with a continuous suture, and invaginated with a Lembert suture, so as not to constrict the lumen of the gut. An elliptical incision was then made in the middle line of the abdomen, entering the peritoneum at the linea alba, and passing upwards so as to excise the entire umbilicus. Through this incision the diverticulum was removed in one piece.

The excess of peritoneal pus was then gently removed and the two incisions closed, a small drainage tube being left in one of them.

Abdominal pain continued for twenty-four hours, and then subsided gradually. There was a little delay in healing of the

wounds, but, when the boy was discharged, they had soundly healed, and the abdominal wall was strong.

On examination the mucosa of the appendix was less inflamed than the exterior; appendicitis was clearly not the cause of the peritonitis.

The removed diverticulum was shaped like an hour-glass (Fig. 1). Its ileal end was no more inflamed than the appendix, but the portion between the constriction and the umbilicus was of a reddish-black colour externally, and its mucosa was correspondingly inflamed. It was tightly distended with pus, and its walls were lifeless, though no macroscopic perforation could be demonstrated.

Microscopy of the diverticulum showed small intestine mucous membrane only.

Comments

(A) *Diagnosis.*—I. There had never been any discharge from the umbilicus in earlier childhood.

II. On more detailed subsequent questioning, it was learnt that the pains of earlier date, as well as the more severe pains of the acute illness, were of a peculiarly "dragging" variety, and always relieved by a doubling up of the abdomen, and made worse by standing erect.

III. In this case a diagnosis of "Peritonitis, probably due to an appendicitis" was made. It is always well in children to bear in mind the possibility of a persistent diverticulum, especially in those cases where there has previously been an umbilical discharge, or in those cases where "dragging" pains in the centre of the abdomen of the nature above noted have been present.

(B) *Pathology.*—This case is an example of a very rare condition—gangrene of a cystic portion of a Meckel's diverticulum.

In Volumes LX and LXV of the *Guy's Hospital Reports* Mr. Turner collected and described all cases of Meckel's diverticulum observed at Guy's from 1885 to 1905, together with some later cases. In only one of these was a cystic condition of the diverticulum noted: serious symptoms were apparently prevented by a fæcal fistula forming at the umbilicus.

It is difficult to explain the mechanism by which the hour-glass appearance of the diverticulum was produced. There were no adhesions, nor any change to indicate past inflammation.

I would suggest that the process of obliteration that should normally occur had started, in this instance, about the middle of the tube instead of at its outer end, and had thus left a patent external portion, which produced the cyst.

(C) *Treatment.*—In this instance it was possible to excise the diverticulum at the original operation. In some cases, as when there is strangulation of the gut by a diverticulum, relief of the obstruction is sometimes all that can be attempted. In such cases a secondary operation should be deliberately planned for the excision of the diverticulum, in view of the many curious and serious complications to which it may be liable if left in the abdomen.

I am indebted to Mr. Turner for permission to publish this case.

MASSAGE AND REMEDIAL EXERCISES IN BONE AND JOINT DISEASES

By W. H. TRETHOWAN, F.R.C.S., Orthopædic Surgeon, Guy's Hospital.

Massage

From the purely physical point of view, for mechanical efficiency of the locomotor system an adequate leverage action is essential. The lever must move easily about its fulcrum, and with a force applied sufficient to overcome the external resistance, or work to be done. All disorders of the limbs are thus separable into those of the *lever* itself (the bone), the *fulcrum* (the joint), the *force* (nerve-muscle), and, to complete the illustration, the *resistance* (*i.e.* static conditions—overwork). But efficiency depends on psychical as well as physical processes, *i.e.* on the effectiveness of the motive force activating the machine, and the relative importance of these components must be clearly distinguished in any case of disability. Physical treatment increases joint movement and muscle strength, develops capacity for co-ordination, and educates the reflexes and the power of volitional control.

Massage (*i.e.* rubbing, as distinct from exercises) is useful only as far as it assists nutrition and mobility. It has only two effects—reflex and mechanical. *Reflex* effect is seen in the relief of pain and spasm by superficial strokings, in a case of acute injury. Surface stimulation is known to cause reflex contraction, and it may be supposed that other forms of stimulation can produce relaxation. *Mechanical* effects result from the application of greater pressure, and are used to influence the circulation of blood and lymph, to mobilise contracted and thickened tissues, and, in the abdomen, to produce a reflex contracture of the unstriped intestinal muscle. The chief "movements" of massage are:—

(1) *Stroking* (Effleurage), which may be superficial or deep. Superficial stroking is done centrifugally, for a purely reflex effect in allaying pain and spasm. Effleurage may be superficial or deep, is centripetal, is done slowly and not forcibly, and is used to aid venous and lymph return.

(2) *Compression*, which consists of several forms of localised pressure :—

Kneading—compression of a superficial against a deep layer.
Friction—very localised pressure with the finger-tips.
Pétrissage—picking up and squeezing the tissues, particularly the skin and subjacent layers.

(3) *Percussion* (Tapôtement), consisting of various methods of beating the tissues.

(4) *Vibration*, done by a machine or by hand, is a method of shaking tissues, for soothing, stimulating, or loosening purposes.

Stroking massage assists venous and lymph flow and improves vascularity; the lighter forms of compression act in the same way. The heavier pressures are used to break up infiltrations and old œdema, assist the healing of chronic wounds and ulcers, and stretch adherent and contracted tissues. Some adherent tissues are best mobilised by "breaking down" under an anæsthetic, but in others only harmful tearing, with subsequent reactionary pain and swelling, would result from this forcible treatment; in the latter gradual stretching by massage is the only remedy, although it can often be assisted by the stretching effect of a splint. In addition to the purely direct effect of massage on the contents of the veins and lymphatics, the mechanical stimulation of the arteriole walls can produce a reflex response, which maintains or restores the tone of the vasomotor system. Percussion is a "stimulating" form of massage, applicable when muscle tone is not greatly deficient. It produces first a reflex constriction of the subcutaneous blood vessels, and, on account of this tonic effect, is useful between and after active exercises; but if unduly prolonged a transient paralytic dilatation occurs—an effect of little worth. A false idea of the value of this stimulation is one of the abuses of massage treatment, for it is fatiguing if misapplied. For the circulation it should be used gently, and it is contra-indicated in general or local fatigue of the nervous system, over contracted or paralysed muscles, and over sensitive parts.

Massage can only assist venous return when the limb and trunk are completely relaxed, and are in such posture that gravity helps; also, the pressure must be light, to limit the effect to the veins alone. Toning up the vasomotor system and assisting the venous return tend to prevent the formation of œdema. In the treatment of recent œdema only gentle pressure is required, but if of long duration greater force is necessary, with the object of making the effused lymph more fluid and

breaking up possible lymph clots. The essentials in the treatment of chronic œdema are—the temporary elevation of the limb; the application of the massage at first to that part of the limb proximal to the œdema, then treating the upper limits of the œdema, and gradually working more and more distally; and the recognition of the supreme value of active exercises of the whole limb, in assisting its circulation and preventing refilling by the œdematous exudate.

The limited utility of massage (*i.e.* pure rubbing) treatment must be recognised, otherwise time and effort are wasted, discredit brought upon the treatment, and often positive harm done by leading the patient to rely wholly on the rubbing, and thus fostering the psychical factor of his disability. It is impossible to "work up" or re-educate a wasted muscle by massage; only active muscular contraction can do this. Massage cannot replace exercise, and is of assistance only in virtue of its effect on the local circulation and mobility. Properly given, massage can relieve the effect of muscle fatigue more rapidly than rest, and it revives the capacity for increased muscular action; but, on the other hand, vigorous rubbing, in misguided efforts at "working up," may be very fatiguing and injurious to weakened muscles. It is to be emphasised that in giving massage treatment the part being treated should be completely relaxed, and that undue force is rarely necessary. The production of a protective reflex from undue stimulation prevents any beneficial result from the massage.

Movements

Painless and unrestricted active movement is essential for the complete restoration of mechanical function. After an acute injury measures to minimise loss of function are as important as those directed to the cure of the damaged structures. Unfortunately, at the present time the masseuse's efforts are largely concerned with the results of neglect of early application of treatment. In the absence of early movement joints become fixed, at first by muscular spasm, and later by the organisation of intra- and extra-articular exudates ("adhesions") and by infiltration and loss of mobility of the surrounding fibrous structures and their postural adaptation to the fixed or deformed position. Hæmorrhagic and inflammatory exudates persist and become organised, and bind and mat together the soft tissues. The muscles rapidly lose their elasticity, waste (reflex and disuse atrophy), and exhibit postural contracture. Early tension and inflammatory pain, and that

due to spasm and displacement (in fractures), gives place later to pain due to pull upon adherent and matted tissues. The local vasomotor system is disorganised, the venous and lymph flow obstructed, and the early inflammatory swelling persists as a chronic obstructive œdema. In later stages the limb becomes cold, wasted, livid, rigid and water-logged, atrophic in every way, and with loss of that muscle and joint sense so necessary for co-ordinated muscular action.

Massage only prepares the part for early movement, in the way already shown. Massage and movement are complementary, and both should begin soon after the injury. In most cases, on account of the relief from pain and spasm afforded by massage, *active movements* are possible at once. They are necessarily light, and of small range at first, but increased as becomes possible without pain. The neighbouring joints are moved as well as that nearer the site of injury, to the greatest extent possible within the painless range. The movements may need *assistance* from the masseuse, either to obviate gravity, or to show the patient what movement is required. The exercises are at first done mildly, gently, and at lengthy intervals, but are worked up in frequency and range as becomes possible, the absence of pain and protective spasm being the signs of safety and the indication for greater progress. A patient is not likely to do early *active* movement to an extent inimical to the repair of the damaged tissues, as pain, the danger signal, is naturally avoided. On the other hand, early *passive movement*, being done by the masseuse and not by the patient, is liable to be harmful if the signs and limits of safety are not observed. The damaged structures are disturbed and repair delayed, thus causing persistence of pain (the most powerful inhibitor of voluntary movement), increase of reactionary swelling, excess of repair substance, and diminution of movement. For these reasons many surgeons *allow* massage and *active* movements from the first in cases of acute injury, but *prohibit* any *passive* work in the first three weeks.

But cases occur in which active movements are impossible in the early stages, or at least until after a little gentle passive motion has been done. Such are met with, for example, in certain fractures, after operations to make new joints (arthroplasty), and in paralysis. In these atrophy and stiffness must be prevented and circulation and repair aided by early passive movements. In some cases passive movements may be safer than active, although given through a wider range. Although passive can never replace active work, it at least paves the way by keeping the injured part supple. The active movements will be added

to the programme of treatment and substitute the passive manipulations as they become possible. For a movement to be really *passive* there must be neither assistance nor resistance by the patient, who must, therefore, be taught to relax completely. He must rest at ease, with the injured part so well supported that there is no apprehension or sense of insecurity. The movements, which must not cause pain, are at first of the slightest, and repeated through that part of the range where movement is easiest and strain least. At one sitting the range is gradually increased in all possible directions. The aim is from day to day to increase the amplitude of motion. At any one treatment the furthest possible *painless* range is procured only once; there is no need to " pump-handle." Passive movement is safe as far as it can be done without provoking a protective reflex contraction, *i.e.* as long as complete relaxation is maintained. The limit of movement possible at one sitting will be that just not sufficient to produce reflex contraction or pain. It is the attempt to move a joint passively when reflex protective spasm exists, which is so fraught with danger. The movement is then no longer *passive*, but resisted by the patient, and therefore becomes a *forced* movement. *Forced* movements applied in early stages of an injury merely steadily increase the trauma, as evidenced by the continued swelling, heat and pain and by the gradual decrease from day to day of the spontaneous voluntary movement already obtained. It must be admitted that the combination of passive and active movements in the treatment of early injury is the ideal one, and will restore function in minimum time, but its application requires a masseuse of great skill. If such skill is not available it is better to forbid passive and rely only on active movements in the first three weeks.

The *early passive movements* described above, which are possible when the injured part is completely relaxed, are to be distinguished from *another form of passive movement* which may become necessary a few weeks after the injury, when the joints and soft parts have, for unavoidable reasons or from the neglect to use active and passive movements early, become fixed. The patient cannot voluntarily overcome the restriction, nor can the masseuse do so without administering considerable force. It may even be that manipulation under anæsthetic is required, to overcome the obstruction. This type of passive movement is more of a "*forced movement.*" It will be dealt with more fully later in this article.

The strength of an active movement should be graduated from day to day to the capacity of the patient. The external resistance that can be overcome will depend on the strength of

the affected muscles. In the earliest stages the patient may require *assistance*, in order to do the required movement without fatigue or strain, and through a greater range than would otherwise be possible. As capacity increases assistance is lessened, and the movement is performed without either assistance or resistance, i.e. *free*, as when the limb is moved in a warm bath, or in some other way where gravity is neutralised and friction reduced to nearly nil. An essential in re-education is to discover some action the muscle can do, however feebly, this being of importance both physically and psychically. Assistance can be given manually, by machines, or by gravity. Most movements of normal life are done against gravity, but postures can be so arranged that gravity may assist movement, or resist, or be neutral; this is the most convenient way of regulating resistance. Day by day the amount of assistance is lessened. It may be that assistance is required in one part of the movement, then gradually lessened, and finally the movement resisted in the more powerful part of the range. The evidence of too great active effort is the occurrence of tremor in the muscles being exercised. In cases where movement is restricted, the capacity for relaxation of the antagonists is important, and it is necessary to secure their relaxation when using gravity to increase the range of action; for example, when it is desired to increase flexion of a knee, or extension of an elbow. If the hindrance to movement is due to causes other than purely muscular, *e.g.* to bone or joint injury, with painful adhesions or infection present, the muscles opposing the movement desired will go into protective spasm as soon as pain occurs. Intermittent passive stretching (as in forcing flexion of the knee by squatting, and extension of the elbow by suspension of the patient from a bar) will be useless, and usually only increases the deformity. Here passive stretching tension can be of use only when constant, as from a splint. In such cases, to secure increased range of movement, the best means is to train, by active exercises, those muscles producing the movement which is deficient—*e.g.* the quadriceps in a flexed knee, and the triceps in a flexed elbow. The same method is also good to apply where movement is prevented by adaptive shortening, and in which, unlike the above group, forced correction is not painful. Here passive stretching would also be applied, as being of benefit, and not likely to make the deformity worse as it would in the painful conditions mentioned above. Thus the antagonists are taught to relax, rather than efforts being made to stretch them passively. One form of active "movement" which is useful, and sometimes the only available, is alternate contraction

and relaxation of a muscle while the joint remains immobile; *e.g.* of the quadriceps when the knee is on a straight splint, or of the deltoid when the arm is on an abduction splint.

Re-Education

The education of a patient to resume the correct use of a damaged part is the final stage in the treatment, to which massage has been a necessary preliminary. Although it is of considerable importance in any particular case to be able to distinguish the truly *organic* factors of the disability from those more commonly regarded as *functional*—*i.e.* the structural damage of the leverage machine from the impaired motive process—yet the distinction is not always very clear, so that confusion may arise as to the respective indications for physio- and psycho-therapy. The attainment of maximum mechanical efficiency depends ultimately on the patient's own will and desire, and on his readiness to co-operate in the treatment, since all that can really be done is to teach him to restore his own function. Mechanical or physical treatment can be regarded as a *passive process*, whereas psychical treatment, which develops the patient's own voluntary effort and initiative, and which is, therefore, much the more important, is essentially an *active process*. Generally speaking, restoration of function is more rapid and complete in proportion as this *passive* or purely physical treatment is reduced in extent and duration. To the patient the importance of active effort should be stressed, but that of the physical adjuncts minimised. There is great danger in allowing him to think he can be cured by what is being done for him. " Passive " treatment—massage, passive movements, splints, appliances, and prolonged rest—cannot restore active function. It should be regarded as a necessary evil, to be used minimally and dispensed with as soon as possible. While serving to protect an injured part and temporarily lessen local disability, these measures are yet liable to lead to more extensive disability, and to a false sense of their worth. Thus a functional defect may be developed quite disproportionate to what might be expected from the original injury. Referring to the injudicious use of massage, Dr. Hurst points out that rubbing a physical defect out of a limb often rubs a functional one into the mind.

But it must be realised that not all structural disability can be overcome merely by an effort of will. Such are definite organic changes involving one or other of the leverage elements, and concerned with the functions either of movement or power.

A joint may be limited in movement and so firmly fixed by adaptive changes without, or alteration of joint surfaces and bone ends within, that an uninjured neuro-muscular system could not possibly mobilise it, especially as the muscles would be secondarily weakened by disuse atrophy. On the other hand, primary organic affections of the neuro-muscular path, at any spot from brain cortex to muscle, might determine an inability to move an otherwise normal joint, whatever the will to do it. Organic disability persists in proportion to the permanent bone, joint, or neuro-muscular damage, but it can be minimised by education, *i.e.* by the development of compensatory actions of neighbouring joints, or by various " trick movements " in cases of permanent motor nerve defects. It must be admitted, however, that many of the late effects of structural damage, wherein organic change is beyond the patient's voluntary effort to overcome, result from the neglect of early activity, with the unnecessary production of adaptive fixation and deformity, and reflex wasting and disuse atrophy. In most cases of recent injury, before muscle wasting is allowed to occur, and after subsidence of spasm pain and swelling which is effected by massage treatment, movement, graduated and allowed with due regard to the bone lesion, is not beyond voluntary power, and should never be permitted to be lost. It is, therefore, in the earliest stages, after the subsidence of the acute symptoms, that re-education of function should begin, or, better, its loss prevented.

Simple passive and active exercises serve to preserve joint mobility, minimise reflex wasting, and assist the circulation; thus muscle bulk and strength is preserved. Re-education implies somewhat more than muscle training, and is concerned with the whole chain of processes involved in the production of a voluntary or of a complex reflex muscular action. The functional defect may be anywhere in the path from the higher centres of initiative and imagination, and of the motor cortex, down to the muscle itself. It may be primarily organic or functional, or a secondary functional element may be grafted on an organic as the result of delay in recovery or of improper treatment. Hysteria, neurasthenia, and malingering are functional defects of the higher centres, and deficiency or impairment of sensory or motor conductivity, disuse atrophy, and loss of muscle and joint sense are functional defects of the lower and subsidiary structures, whose results may far outweigh those of an initial organic lesion. Through the neglect of treatment and the occurrence of disuse atrophy a patient may in a few months forget how to get an impulse down to a muscle, even though the

organic defect is sufficiently recovered from to make this structurally possible. To maintain skill in the performance of a complicated movement constant practice is necessary; otherwise the movement deteriorates. With inability to perform a movement, the sense of it is soon lost, and then the method of its production is forgotten. In organic paralysis a real obstruction exists somewhere in the path from brain to muscle, which may possibly be recoverable. Disuse of other muscle groups need not necessarily supervene, but if it is allowed to do so, the obstruction to voluntary action is thereby increased, as it is still more by the deterioration of joint sense and of the muscle sense of the antagonistic group, which further result from the loss of movement. The power of co-ordinated movement disappears after any inaction, especially when due to injury. Circulation is impaired by loss of movement, and disuse atrophy of the limb increases, in vicious circle. In bone and joint lesions the picture is much the same, with reflex atrophy added. The disability directly resulting from the initial injury, unless combated by treatment, promotes loss of movement and weakness in the remainder of the limb, thus adding the symptoms of a functional paresis. It has been mentioned that re-education cannot begin too early after the subsidence of acute symptoms, even though its application might be partly hindered by splints necessary to maintain position and prevent further injury. The patient can exercise his muscles by contraction even when the limb is splinted. The indication is to keep the limb in as normal condition as possible, with adequate blood supply, in spite of the lesion, and not allow it to suffer on account of the temerity and passivity of the surgeon or patient. What function remains should be cherished, otherwise it too will soon disappear. Atrophy from disuse is often more difficult to overcome than that due to direct injury or to reflex effect. The presence of atrophy, lack of movement, and poor blood supply may have a bad moral effect on the patient, inhibiting his efforts and lessening his ability for self-improvement, whereas evidence of vitality and restoration of movement are encouraging, and the best incentives to him to work the harder.

Muscular re-education is, therefore, the process whereby physical and psychical training in mechanical function go hand in hand. Actually it is the education of co-ordination of the simpler muscle actions into the complicated processes which become the ordinary voluntary actions—or, by dint of regularly repeated voluntary effort, reflex actions—of ordinary life. It begins as early as any movement, however little, is possible after paralysis or injury, and it is necessary as long as any

further strength or skill is required in any particular action, or until the movement becomes automatic. When a muscle is weak and just able to move, the active movements must be of small range, against little resistance—or possibly even assisted, and frequently repeated. Periods of massage are interspersed with the movements in these initial stages. Graduation of effort is at first provided by increasing the frequency and range of contraction, and later by holding the muscle in contraction for a time. This frequency and extent of effort is graduated throughout the training, and a convenient way of effecting this is by utilising gravity, which can be arranged at first to assist, or be neutral, or later to resist the movement desired. A muscle may have insufficient power to sustain a contraction throughout a certain range, but might do so if assisted. It may be necessary to teach the patient what movement is required by demonstrating it in the opposite limb. In some cases co-ordination may have failed so much that the patient is unable to relax the antagonist, in which case the contraction of the opposite muscle is impossible. An antagonist does not antagonise, but co-operates and co-ordinates. Its action is a voluntary graduated relaxation, giving stability and co-ordination in the movement being trained. Therefore voluntary relaxation must be taught simultaneously with voluntary contraction. It is not necessary to prevent all action antagonistic to a weakened muscle, in the fear of over-development of the antagonist; the training of co-ordination requires the reciprocal action of both groups, and it is sufficient merely to prevent over-stretching of the weaker group. It is important not to overdo the training and fatigue the muscle unduly in the early stages, and sufficient rest should be allowed between the exercises and between the periods of treatment. Frequent light efforts are of greater use, as well as less fatiguing, than a lesser number of more strenuous movements. The patient should be told what and how much exercise to do in the intervals of treatment. The early sign of fatigue is muscular tremor. In great fatigue the muscle may be totally unable to contract; in the effort to continue the movement other muscles are called into play, leading to inco-ordinated, exaggerated, and false action. Volitional impulses are directed to producing group movements and not actions of individual muscles. If when a particular movement is willed the "prime movers" (Beevor) are paralysed or inert from over-fatigue, the "synergist" muscles—those giving subsidiary aid in the prime action—endeavour to fulfil the movement, but often not very successfully. If the effort be continued, with much straining, other groups, the antagonists, and the "fixative" muscles of all the

neighbouring joints, come into action as well, giving a wasteful inco-ordinated and widely distributed contracture of no use whatever in muscular re-education. Any voluntary effort must be purposeful to be useful in training. It is therefore essential that the movement being trained should be limited to the action of the muscle and its antagonist only, and that the posture be such that no undue strain is involved. Another sign of over-activity is a diminished power or range of action instead of progressive increase. All weak muscles should be prevented from being over-stretched, both during active treatment and in the periods between, when light splints are supplied to maintain a posture in which stretching by gravity is prevented. But it is not necessary to maintain absolute relaxation of paralysed muscles, otherwise adaptive shortening and loss of elasticity occur. Movements may be allowed in the inner half of the range of action. This restriction need not prevent the movements necessary to preserve the general fitness of the rest of the limb—its circulation and nutrition, joint and muscle sense, and co-ordination. It cannot be expected that repair and restoration of function can be rapid when this has been neglected.

At first movements may be free, or assisted or resisted manually by the masseuse. At a later stage in the training the various apparatus of the gymnasium will be utilised—such as weights and pulleys, poles, cycle, rollers, rotating machines, and ladder bars; by these assistance or resistance can be regulated. When special apparatus is not available, use can be made of domestic furniture, or of free-standing exercises. Gradually the exercises are made more strenuous and complicated. The continued variation of the exercises, and especially the gradual increase in the effort entailed by them, are important. Occupational and technical exercises, in the performance of some useful, interesting and productive work, are of great utility later, in their special attraction to the patient. In conditions of the lower limb, re-education of the essential functions, such as walking and foot-drill, dancing, and running, will complete the training. Class exercises are very helpful, on account of the spirit of emulation fostered, and as a means of dealing with patients in quantity.

Recent Injuries

The importance of the early application of physical methods of treatment of injury is becoming increasingly appreciated. The period at which it is prescribed depends on the nature and severity of the injury and on the practice of the surgeon, who may often be adversely influenced by a lack of knowledge of

the facilities available, or by temerity. Dislocations and injuries of soft parts are more commonly sent for massage treatment earlier than recent fractures, where splintage and the fear of recurrence of deformity add difficulties. Healing of damaged tissues can go hand in hand with the restoration of their use, and the two processes are mutually helpful. An unwarranted conservatism creates a lot of convalescent lee-way to be made up, and vitiates many a result. It is the acute case which benefits most from physio-therapy, and in which this expensive treatment is economically of most value. When treatment is unduly delayed the efforts of the masseuse are devoted largely to combating the results of neglect—poor circulation, disuse atrophy, loss of power, stiff joints, contractures, and adherent scars. A confusion of ideas as to the utility respectively of massage, passive, and active movements, and the unnecessary difficulties for the masseuse which these neglected cases create, are liable to produce a sense of disappointment and bring unjustifiable discredit upon massage treatment. They are also the *raison d'être* of lay practitioners, who realise the necessity for active exercises as much as they appreciate the importance of a joint being completely mobile and painless. The presence of septic infection, open wounds, and ulcers is often said to contra-indicate physical treatment; but this attitude is too conservative, and in most cases incorrect. Healing of wounds and eradication of sepsis is not only hastened, but the associated mobile structures, such as muscles, tendons, and ligaments, are prevented from becoming permanently matted and fixed, as they are so prone to be in the delayed healing of an open septic wound.

Symptoms and pathology of injury.—Swelling is at first due to hæmorrhagic infiltration from the torn ligaments and raw bony surfaces, and to hæmorrhagic effusion into the joint and tendon sheaths. Soon the swelling is increased by reflex vasomotor disturbance, which causes a widespread œdema. Through absence of voluntary muscular action the veins become engorged, the circulation slow, and transudation increased by the venous stagnation. Nutritive changes, vitality, and reparative power are lowered. Mechanical obstruction, from displaced fragments or constricting splints, may also exist. *Pain* is due to the tension exerted by the effusion, and to spasm and cramp. Spasm is a reflex attempt to immobilise damaged surfaces, in the effort to lessen pain and prevent further injury; it is greatest when fixation is least, as shown by the relief which splints afford. *Wasting* and *weakness* are initially also a reflex effect, resulting from tension and pain in the joint. A joint receives the same

nerve supply as the muscles controlling it. Bankart (*Proc. R.S.M.*, 1925, Vol. XIX) suggests that two factors are responsible for "reflex" atrophy; the one a reflex inhibition of the postural or tonic activity of the associated muscles, and the other a reflex excitation of phasic activity of the same muscles, *i.e.* an attempt at reflex protective spasm. Continued effusion within a joint stretches the capsule and makes the joint lax and unstable; this instability is further promoted by the muscle wasting which the effusion favours. Thus is increased the liability to weakness, recurrent effusion, and internal derangement, a condition particularly exemplified in the knee joint.

Fractures

In considering the degree of application of mobilisation treatment, the extent of mobility and the position of the fractured bone ends are of more importance than the damage sustained by the soft parts. The treatment is much the same in all acute injuries, but the "dose" is determined by the quality of the bone injury. A fracture in good position, with fragments so interlocked as to be undisturbable by early movements, would count in treatment rather as a sprain, except that progress to strenuous function would be slower, since consolidation takes twice as long in bone as in soft tissues. The point is of greater importance in leg injuries, as a sprain would walk from the first. Certain clinical conditions, in relation to mobilisation treatment, must therefore be considered.

Simple fractures without initial displacement.—Many fractures are merely cracks or fissures, transverse or oblique, and have never been displaced, the violence having been insufficient to tear the periosteum to any extent; soft part laceration is minimal. Such are often found only on x-ray examination, and clinically are liable to be mistaken for bruises and sprains, or diagnosed as "synovitis" when near joints—the latter particularly in the elbow joint. Local effusion is not great, and union rapid enough to obviate any serious risk of displacement within a few days. They can be treated merely as sprains, and splints are unnecessary. There is less risk in proportion as the fracture is spiral and not transverse. Greenstick fractures usually come within this category, but occasionally in these there is lateral instability, and angular deformity which may require preliminary correction and a retentive splint. The risk of twisting strains or weight-bearing, in simple fissure fractures of the leg, would prevent walking for three or four weeks, and in those of the thigh for six weeks. Fractures of the *tarsal*

bones, in which there is usually little displacement unless the injury is a direct crush, are treated as sprains, but are more serious in that the fracture usually extends into a joint. Weight-bearing is inadvisable for six weeks, to allow the damage to the joint surfaces to heal; a tedious painful traumatic arthritis is very liable to occur, and would certainly be precipitated by premature weight-bearing. On the other hand, the treatment of *carpal* fractures is quite different from that of sprain; this on account of difference in natural mobility of the wrist and foot. An intra-carpal fracture is often mistaken for a sprain. The early activity necessary for a sprain would ruin any chance of union of a fractured scaphoid, for instance, which, should the fragments be in perfect position, will unite only if the wrist joint be immobilised for three weeks. Premature movement in such a fracture only hastens the advent of traumatic arthritis.

Impacted and interlocked fractures.—Impaction is an implantation of one fragment into the other, without possibility of movement occurring except by considerable force; the receiving fragment is usually comminuted. It can occur only by a force exerted at right angles to the line of fracture. The term is used too loosely, and often applied to an irregular transverse fracture where the fragments are not really implanted but are spiculated and merely interlocked. Both conditions are more prone to occur in the cancellous tissue near joints. Most so-called impacted fractures are merely interlocked, and differ from true impaction in that angular motion at the line of fracture is free and that lateral stability is also likely to be disturbed by anything more than the slightest force. In these fractures, examples of which are to be found in most cases of Colles' fracture and of fracture of the surgical neck of the humerus, movements within the first few days following the injury are more prone to occur at the line of fracture than in the associated joint; whereas a truly impacted fracture will not yield except to forced movement under an anæsthetic—*i.e.* disimpaction. The firmer the impaction the greater the deformity, which may be sufficient to require disimpaction, although it is often left undisturbed and respected as the fortuitous occurrence of the first stage of repair. Certainly, comminution in any fracture is conducive to early consolidation. Contrary to what is taught, impaction never occurs in intracapsular fracture of the neck of the femur, but is common in "extracapsular" fracture, where the base of the neck of the femur is driven into and comminutes the great trochanter region, as the result of a direct blow on the trochanter. Impaction is extremely rare in fracture of the surgical neck of the humerus,

and in Colles' fracture, although often said to occur; the anatomical conditions and the line of action of the force causing these fractures are such that real impaction is well-nigh mechanically impossible. True impaction occurs at other sites where "end on" violence is possible, as in "crush" fractures; for example, in the os calcis, in crushing of a vertebral body into the adjacent one, in transverse fracture of the tibia just below the tuberosities, and sometimes in association with T-shaped fractures of the lower ends of humerus and femur. Impacted fracture of the great trochanteric region always unites, whatever the age of the patient, in contrast to the intracapsular variety, in which bony union is exceptional. In the other situations an impacted fracture is of far less importance as a fracture than as a cause of damage to the neighbouring joint, which will henceforth be the seat of chronic mechanical arthritis, with its interminable pain and stiffness. If impaction is preserved, the masseuse can begin treatment as at a stage at which moderately firm union has occurred, *i.e.* as saving two or three weeks of the acute stage of initial disability. But in a fracture merely interlocked, as after reduction in most cases of Colles' and surgical neck of the humerus, greater precautions as to early movements will be necessary. In some no splintage will be required from the first, and relaxed passive or even active movements are possible in the wrist or shoulder within the next days following injury. In others there may be greater instability, and various degrees of splintage or fixation thus required for a few days before movements would be possible in the neighbouring joint.

Fractures with gross displacement, as of the shafts of the long bones, and some cases of severe fracture-dislocation—*e.g.* in the ankle, present great difficulties in the early application of mobilisation treatment. Many are submitted to open operation, after which the difficulty is lessened, but if operation is not done the necessary retentive splintage may prevent anything but a limited application. Advocates of early mobilisation restrict splintage to the very minimum, holding that union in a good position is of less importance than the production of a strong mobile limb. On the other hand, the desire to maintain perfect correction in spite of everything may lead to close confinement of a limb for six or eight weeks, with no mobilisation whatever. The safer middle course is now generally adopted, and splintage is so designed that the neighbouring joints can be daily mobilised to some degree without risking the position of the fragments; or it is arranged that part of the splints can be removed with safety while the treatment is being done. Most

fractures of the femur and of the upper part of the tibia in which, in addition to splintage and suspension, gradual traction is required for the correction of shortening and alignment, are put up by the Hodgen method, but with weight and pulley instead of a fixed extension. A hinged leg-piece allows the knee to rest in the flexed position (thus guarding against backward angulation of the fragments) and the joint to be moved daily through a considerable angle. Much of the limb surface is accessible for massage treatment, the extension strapping forming no hindrance. The foot and ankle can be moved, and the counterpoised splint allows all movements of the hip, except rotation, through a considerable range. When there is very little tendency to overlapping and lateral displacement, the best general method is that of the " bivalve " plaster of Paris splint. Applied under an anæsthetic, with the limb fully corrected, and with minimum upholstering, the plaster is immediately cut down along the anterior and posterior middle lines (or along the sides if desired). Massage begins within a day or two. One half of the plaster is removed, the limb laid on its side resting in the other half, and the treatment of the exposed half of the limb is carried out; the half plaster is then applied, the limb turned over, and the treatment repeated on the second side. The limb is not completely removed from the plaster for the first week or so, *i.e.* until the granulation tissue is firm enough to prevent displacement of the fragments. This method is applied to fractures of and near the knee and ankle joints, and in many cases to fractures of the shaft of the humerus and forearm bones. The initial deformity of a recent fracture is due chiefly to the original fracturing force. Lateral distension of the inextensible fascial compartments of the limb (the " longitudinal ties ") by effused blood and lymph assists in maintaining the shortening of the bone, as does also the reflex muscular spasm. The two latter deformity factors are directly combated by the massage, and the reduction of the original deformity is facilitated in consequence; it is thus oftentimes preferable to give a few days' treatment preliminary to the completion of the reduction under anæsthetic. Many surgeons now adopt as a routine the method of gradual reduction by massage and mobilisation treatment.

Effect on union of movements at the site of fracture.—Union is undoubtedly assisted by slight movements of the fragments at the site of fracture, especially if the strain is longitudinal, or " end on "; but lateral movement must not be excessive. The irritation of the fractured ends promotes callus formation, which is conducive to repair. In cases of delayed union of the femur or tibia, consolidation is hastened by allowing some

degree of weight to be transmitted through the fracture, provided that lateral movement is prevented by side splints. On the other hand, in fractures which have been treated by "plating," and in which, therefore, end-on strain through the bone is impossible, the small amount of callus formation and the liability of the fracture to yield, if the plate should break or the screws loosen, at a stage when firm consolidation might be expected to have occurred, illustrate the ill effect on union of absolute immobility. This point should be remembered in carrying out mobilisation treatment after a plating operation. In adults delayed, or even non-union, is not uncommon in the humerus and forearm bones (especially the lower part of the ulna). This is due to the great difficulty in maintaining sufficient immobility in a lateral direction, and because a "weight-bearing" type of thrust is more difficult to apply in the upper limb; in fact a negative pressure may often obtain in the humerus, as over-traction is difficult to avoid unless the patient be confined to bed. Liability to delayed union is greater in transverse fractures without comminution. Oblique and comminuted simple fractures always unite in normal time if they are in reasonable position.

But instances occur where anything but complete immobilisation is detrimental to the consolidation of a fracture by bony union. These are found at situations where little or no ensheathing callus is thrown out. Intracapsular fracture of the neck of the femur will never unite, either by bone or fibrous tissue, after the age of forty-five or fifty, if treated in the usual way by Hodgen's method, however accurately the apposition of the fragments be maintained during eight weeks' recumbency; whereas complete immobilisation of the hip and leg, with the limb abducted and internally rotated, in a plaster of Paris spica, although a tedious treatment for patients of this age, does undoubtedly result in bony union in some cases. The reason for the failure of the Hodgen method is that it allows some movement at the site of fracture, in virtue of the close proximity of the hip joint, in which movements are permitted by this splint, although the freedom from pain throughout the recumbency stage would seem to negative the possibility of movement at the site of fracture. Possibly the negative interosseous pressure, due to the traction, would explain the absence of the pain which might be expected to occur by the mutual friction of the fractured surfaces. Fractures of the patella, and many cases of fracture of the olecranon process will not unite by bone unless the fragments are kept in complete and immobile apposition. Unlike the hip fracture, the alternative in these cases is

a fibrous union. Fractures of the scaphoid bone of the wrist often do not unite, although apposition of the fragments may be excellent. It is said that the presence of synovial fluid inhibits callus formation, an opinion probably based on the examples of the neck of the femur, olecranon and patella. But it is more likely that the important factor predisposing to non-union of the scaphoid bone is the want of sufficient immobilisation, the consequence of the frequent non-recognition of the presence of this fracture, as little trouble is experienced in the non-union of fractures involving other joints. If synovial fluid is responsible for the failure of union by bone, why should the bone unite by fibrous tissue in the patella and olecranon, and not at all in the neck of the femur?

Fractures into joints are of far more importance as joint lesions than as fractures. Ultimate joint function depends before everything on the complete restoration of the bearing surfaces, and the accurate relationship of the apposed bone ends. There must be no " steps " or irregularity of contour in an articular surface, nor even merely a subluxation, if recovery of joint function is to be complete. Otherwise the permanent derangement will lead to premature breakdown of the joint from " traumatic " arthritis, the incidence of which, after injury, is proportional to the extent of the derangement and to the age of the patient. Traumatic arthritis is nothing more than mechanical derangement of a joint, and its effects are analogous to those produced on continued use of a damaged hinge or other " bearing " in a machine. Therefore most joint injuries with displacement of articular surfaces will require operative reconstruction before functional treatment can be undertaken. After the operation massage and mobilisation should start immediately, the case now resembling one of sprain. The symptoms of a developed traumatic arthritis are the usual ones of over-activity —pain, swelling, and increasing restriction of movement; the treatment is rest and restriction sufficient to allay the temporary irritability, and a nursing back to its optimum efficiency by massage and mobilisation carried out as for a simple sprain and synovitis.

Mobilisation treatment of fractures in general.—At first comparative immobility of the limb must be secured by some slight support sufficient to ease pain and favour muscle relaxation. No extensive splintage may be required for the first few days, especially if it be desired to reduce the displacement gradually. The posture of the limb and the manipulations necessary in treatment must be such that the fractured surfaces are not moved on each other when the part relaxes. The first indication

is to relieve pain and spasm, to assist circulation, and to remove local swelling and stasis. The reflex disturbance of the circulation—the cause of the widespread œdema, and the pain, spasm, and cramp, are counteracted by light stroking, done slowly, gently and rhythmically, in a centrifugal or centripetal direction, over the whole limb. As the tissues become softer the localised exudate becomes more palpable. If the spasm does not yield to stroking alone, gentle rhythmic kneading is done in a centripetal direction. The relief of the spasm facilitates the reduction of the displaced fragments. To assist the venous and lymphatic return deep stroking is done centripetally, and to combat the œdema and hæmorrhagic infiltration kneading and deep stroking alternate. The limb is always emptied upwards by the massage strokes. The proximal part of the swelling is first attacked, and successively more distal portions are then engaged, each portion of swelling being, so to speak, softened, detached and pushed in a central direction up the limb. Thus the proximal parts of the limb are massaged alternately with the successive portions of swelling. The kneading prevents further effusion, and hastens the absorption of what already exists before it can become organised. The site of the fracture is not kneaded, or only the lightest pressure exerted, but the limb distal to the fracture is treated in the same way as the proximal part. No friction is done. The massage, by its intermittent muscular pressure, is the closest possible imitation of the physiological maintenance of the normal circulation.

The second indication is to restore the circulation and assist repair, by voluntary movements to prevent reflex muscle wasting; and by movements, active and passive, to preserve joint movement and sense. The movements will not displace the fragments if allowed in extent and duration with due regard to the position of the fracture and the line of action of the muscular force. If movement is natural and painless no strain is exerted on the torn tissues and fractured surfaces, and their repair is not hindered. It is the first movements which are the most difficult and the most important. When relaxation is produced, the gentlest passive movements are begun, at first in the neighbouring joints and a little later in the damaged joint itself. The range of movement, at first very slight, is gradually increased during the séance and in subsequent treatments, but must be short of producing pain or reflex muscular spasm. Movements in directions likely to displace the fragments are postponed. Voluntary movements both in the neighbouring and the affected joints are encouraged from the first, but may be impossible for a few days in the damaged joint itself until it

has first been mobilised passively. The early voluntary movements are at first slight, and may require assistance, the one hand of the masseuse supporting and taking the weight of the limb segment, while the other steadies the site of the fracture. But the voluntary movements will steadily increase in range as the patient gains more confidence and finds himself able to do them painlessly. Treatment is undertaken daily, with increasing degrees of movements. Between these periods the patient is advised to continue the movements of those joints of the limb which are not restricted by the splinting. Even when the splints keep a joint fixed, active contraction and relaxation of the muscles controlling it may yet be possible, and so serve to prevent atrophy and to assist the venous circulation.

In a Colles' fracture, for example, when completely reduced, and with no tendency to displacement of the lower fragments, and in which splints are merely protective and not retentive, the splints may be removed on the first day and gentle passive movements of the wrist done when the muscles are quite relaxed. Active movements may not be possible for a few days in the wrist joint itself, but will be in the hand and fingers, elbow and shoulder, both during and in the intervals between treatment. The amplitude of passive range in the wrist, rotation as well as flexion and extension movements, are increased daily, as rapidly as the freedom from response by pain or protective spasm allows. If displacement of fragments is likely to occur, removal of the splints may be impossible for a few days, when the wrist must perforce be kept immobilised, and the application of treatment limited to the accessible parts of the limb. Again, in fracture of the surgical neck of the humerus, the inception of movements in the shoulder joint will be determined by the stability of the fracture after reduction. In some cases the gentlest of active movements, *e.g.* slight swinging of the arm in extension and flexion directions, are possible within a day or so of the injury, when even passive movements in relaxation would be unsafe. In others the tendency of the lower fragment to slip forward would necessitate immobilisation of the shoulder joint for a week or so. When union is progressing normally, and when the shape of the fractured ends are not such as would render them mechanically very unstable, the granulation tissue which precedes the callus formation is in about seven to ten days organised sufficiently to maintain reduction. At this stage assisted voluntary movements would be quite safe. In fracture of the surgical neck of the humerus movements of the elbow and of the limb below this would be encouraged from the first, even though the shoulder needed to be kept fixed.

From the time when recurrence of displacement is not, with ordinary precautions, to be feared, the treatment of a fracture is similar to that of any injury of the soft parts, except that progress is less rapid. Each day the active movement is increased in range and power as the absence of pain and spasm permits. The early passive movements in relaxation will cease as the range increases, and as a greater painless active effort becomes possible. Massage will continue throughout until union is firm. The light stroking gives place to deeper stroking and kneading. The fractured site, at first avoided, is approached gradually as it becomes less tender. There is no need for massage when the range of movement is complete. No movements tending to cause displacement are permitted until union is firm. By the end of the second week, or maybe before, simple exercises with apparatus can be started, such as rollers and rotator machines in lower arm fractures, and in the upper arm by means of weights and pulleys, the weights at first assisting by neutralising the effect of gravity. Simple ordinary actions may be allowed. Arm cases will get about from the first. Leg cases will walk on crutches after the first week or so. Fractures of the thigh will require longer recumbency, perhaps for six weeks or more, but the earlier simple exercises can be done while the patient is still in bed. Gradually the strength of the exercises is increased. As the time approaches the fourth week, when bony consolidation is becoming complete, exercises against greater resistance are possible, and carried out by means of weight and pulley apparatus, wall bars, ladders, etc. Finally, ordinary games and technical movements are permitted, *e.g.* cycling, rowing (on machines in the gymnasium designed for these purposes), type-writing, piano-playing, etc. In a general way, upper limb fractures should have full movement of joints and a fair degree of power in four weeks, and lower limb fractures able to take weight in four to six weeks.

The tenderness at the site of fracture is inversely proportional to the degree of consolidation, and disappears when this is complete. An increase of sensitiveness during treatment signifies that the callus is being strained, and that activity is being overdone. Other unfavourable signs, as denoting excessive use, and as observed from day to day, are increase of pain, local swelling, and stiffness, and diminution of the range of voluntary movement in the associated joints. These call for more rest and a less ambitious rate of progress. A little pain may occur during the earliest efforts at active movement, more especially if no preliminary relaxed passive movements have been given or if no treatment has been carried out within the

first few days or weeks after the injury. Even slight voluntary effort may be painful for a wasted muscle, but it is a harmless pain and of no significance if it passes off after half an hour's repose. Therefore, in estimating the significance of pain, it should be considered in relation to the other danger signals mentioned above.

That the most important consideration in the treatment of a fracture is the perfect apposition of the fragments is a view from which the pioneer advocates of treatment by early mobilisation dissented, holding that it diverted attention from the still more important principles of maintaining joint mobility and preventing muscle wasting. Wharton Hood says that if the surgeon take proper care of the muscles, the injury of the bone may almost be left to take care of itself. They held—and up to a point it is true—that as the spasm and swelling subside with early treatment, a gradual reduction of displacement becomes possible in the first few days following a fracture, often more effectively than by reduction under an anæsthetic without any preliminary massage treatment. A few days' previous treatment cannot be but a great advantage, even if reduction under anæsthetic is deemed necessary. It is axiomatic that the possible degree of recovery of function must be greater in proportion to the accuracy of the restoration of structure, and that the ideal method of treatment must be that which has equal regard for both aspects of the question, and in which the functional result will be commensurate with the pains taken to restore alignment. The immediate functional result in any particular case may be excellent, although the bone is badly aligned; but the result must also be considered from the point of view of its future effects, years after the original injury, when, in response to altered skeletal shape and function, other structures react ineffectually and wear out prematurely. The altered stresses through the bone, the result of its mis-shape, fall on the neighbouring joints, and are bound eventually to produce arthritic changes. In this broader sense, therefore, there can be no such thing as a result being perfect functionally and poor anatomically. In modern times the general public, with its free access to skiagraphy and its keen appreciation of the economic disadvantage of disability, demands, as Arbuthnot Lane has pointed out, a high standard of structural restoration as well as function. There is no reason whatever why the best methods of correction of the deformity should not be combined in treatment with those promoting early activity, and so give us the maximum return of function, and that in minimum time.

Sprains and Dislocations

Pathology and treatment.—Two generations ago a strain was regarded as an injury far more serious, in its longer duration of incapacity and less complete recovery, than a broken leg. Sprains are divided into two groups. In the *first*, the joint is wrenched in a certain direction completely beyond its ordinary amplitude, the muscles naturally opposing the movement in that direction having been caught completely off their guard. Ligaments are ruptured, or their bony attachments torn away. Anything might happen—sprain, fracture, dislocation, or fracture-dislocation. In the *second* group, the initial violence is less severe, and, further, the antagonistic inhibition of the forced movement is partial only; the strain falls on the neighbouring muscles and tendons, instead of on the ligaments. Sprains are commonest in the ankle, knee, wrist, and thumb. In a dislocation one or more ligaments and a portion of the capsule are torn, as well as the synovial membrane. The injury is usually confined to these structures (but *vide* the article on traumatic synovitis). It is advisable to give an anæsthetic for the reduction of a dislocation, as the displaced bone can be more easily manipulated to retrace its path when the muscular spasm is overcome. Preliminary massage, by allaying spasm, may obviate the necessity for an anæsthetic when reducing a dislocated shoulder. Spasm subsides after reduction, and voluntary movements are possible from the first. The old treatment of dislocation entailed several weeks' complete immobilisation of the joint, which resulted in great stiffness from adhesions, and marked atrophy. The adhesions required to be broken down later under anæsthetic; such joints formed a good proportion of the cases dealt with by bone-setters.

A dislocation, when reduced, is merely a severe sprain, and the treatment for both follows the lines laid down for fractures, the progress being, however, more rapid. The principles of treatment are to stop the increase of swelling, to get rid of what there is as soon as possible, and to start active movements immediately to ensure the prevention of adhesions and atrophy. Slow superficial stroking relieves the pain, and afterwards deeper stroking and kneading inhibit swelling and hasten its absorption. Firm compression, by bandaging evenly over a thick layer of wool, is at the present time employed during the first day or two, with two objects—to prevent further swelling, and to prevent lateral distension of the skin so that active movements may the better assist the local circulation in the damaged part of the limb. Formerly, linen strapping was

used, and applied to give support without compression but yet allowing joint movement. Active movements of the injured joint are permitted from the earliest, providing the torn structures are not subject to tension. Ordinary use, *i.e.* without the exhibition of great force, becomes quickly possible through a considerable range without harmful strain. Pain on movement will be the guide. What is required in the early stages is to avoid putting the joint into the extreme range where the injured ligaments become really stretched. Up to this point the muscles, unless they themselves are damaged, will check any tendency to re-dislocation. Massage is continued daily as long as any swelling remains, or until it can no longer assist in easing movement. Active movements which might predispose to displacement are held in reserve for a few days, and then assumed discreetly; movements in the other directions are freely encouraged from the first. The special muscle groups preventing dislocation, or protecting the joint against any position of chronic subluxation, may require special attention, *e.g.* the quadriceps in the case of the knee, the adductors of the shoulder joint, and the peronei in the case of the ankle. The limb in general is treated, as well as the damaged joint. Recovery from sprain or dislocation should take about ten to fourteen days. A patient with a sprained knee or ankle must be encouraged to walk from the first, or at most within a few days, and to disregard any pain that may occur.

Minor sprains.—The lesser degrees of sprain are liable not to clear up completely but to lead to minor disabilities which are protracted and irritating, and which may later require forced movement under anæsthetic for their cure. These are cases which may not have been taken seriously by the patient at first, or by the medical attendant later, and which are liable to seek the help of bone-setters. The usual symptoms are—attacks of pain on certain actions, spots of local tenderness, recurrent attacks of slight effusion, weakness and a tendency of the joint to "give" unexpectedly in certain positions. Usually a slight restriction of movement in the direction which stretches the originally torn ligament can be detected, and pain is felt when this movement is made passively, but in others there is no restriction whatever, although pain is felt. The trouble in these cases is due to adhesions restricting the independent mobility of the several soft structures in and about the joint which were involved in the original damage.

Bruising of articular cartilage; "stubbed joint."—The indirect or laterally applied violence causing sprain injuries usually spares the articular cartilage from injury, but direct

pressure transmitted along the axis of a bone, as to the shoulder in a fall producing a Colles' fracture or by a blow on the point of the shoulder, or, again, in the case of the hip, by force transmitted from the great trochanter, may bruise the cartilage on one or both articular surfaces. The same condition occurs in the knee from direct blows sustained by the condyles of the femur; in the ankle at the front border of the external malleolus, from impaction of the outer surface of the astragalus upon the malleolus in an abduction-eversion wrench of the foot, which violence might otherwise have produced a Pott's fracture; at the posterior end of the sub-astragaloid joint, in the tubercle or os trigonum region, from a forced plantar flexion injury; and in the joint between the inner cuneiform and the base of the first metatarsal. The condition is possible in most joints; in some the damage is incurred at the articular edges, in which case the symptoms in the joint are local; but in others the more deeply situated portions of the cartilage are injured, with pain and restriction involving the joint more generally. Articular cartilage is avascular, and the injury depends for its healing on the ingrowth of vessels from the articular edge. The symptoms—so typically seen in "stubbed shoulder" associated with Colles' fracture—are of late onset, arising about three or four weeks after the injury; the patient begins to complain of pain in the shoulder and arm, and spasmodic restriction of movements occurs, and these symptoms are made worse by mobilisation treatment. If accessible to palpation—as is possible where the damage is at the articular edge—there is acute tenderness on local pressure, and pain is felt on the reproduction of the movement which originally caused the impaction of the two edges or surfaces on each other. The condition is easily distinguished from "adhesions," in which pain is produced by passively forcing the joint into the extreme position which stretches the damaged ligaments; it is the opposite movement, impacting the joint on one side, that would be painful if the articular edges were bruised. Absolute rest, for some weeks or even months, is necessary for a bruised or impaction cartilage injury, otherwise pain persists indefinitely, and finally the cartilage becomes locally eroded and exfoliated, with grating occurring on movement. The possibility of such cartilage injury determining the onset of monarticular (osteo-arthritis) of the hip joint in elderly subjects who have sustained a fall on the buttock some time previously, is discussed in the article on traumatic synovitis.

Synovial fringes.—A sprain-like injury of a joint may fall particularly on a synovial fringe, which becomes suddenly

pinched or squeezed. Irritation of the congested and painful fringe by the repetition in ordinary activity of the movement which, when excessive, produced the condition, may be a cause of continued pain and swelling. This injury is more prone to occur in joints already deranged by chronic arthritis, as in these the fringes are already hypertrophied and the articular edges sharp from osteophytic formation. The symptoms are local tenderness and swelling, and increase of pain in the direction of compression of the fringe, with relief by the opposite movement. The direction of the movement that elicits pain serves to distinguish the condition from "adhesions," but apart from exploratory operation it is difficult to diagnose a nipped fringe from an impaction cartilage injury when either occurs, as they may do, in an otherwise normal joint. A cartilage injury will necessitate a longer period of rest for its recovery than a damaged fringe. In the common class of fringe injuries in old arthritis joints, if acute and very painful, absolute rest for three weeks is necessary; when the condition is more chronic, as, for example, in the congestion and painful swelling of the fat pads subjacent to the ligamentum patellæ, in chronic arthritis of the knee, walking may be possible only in an appliance which prevents the joint movements from just coming within the painful and irritating range; such, for example, is the Marsh's "knee cage." The hindrance to movements caused by hypertrophied synovial tissue, and its vulnerability, is one of the causes of continued disability in old arthritic joints, in many of which the infecting process is long since dead. In any infected joint it is most important accurately to apportion the symptoms to the two factors—the infecting process, and the mechanical results of such process; often the line of demarcation is not clear. Many chronic arthritic joints, especially in the case of the knee, are considerably improved in ability and function by a wholesale extirpation of irritable and redundant synovial tissue by open operation.

Traumatic synovitis is a clinical condition in which, in the acute stage, the joint is distended with blood; and later, when subacute or chronic, is swollen from thickening of the synovial membrane and a variable amount of serous effusion. It results usually from one of the severer types of sprain, involving not only an extensive rupture of ligaments but also injury of the synovial membrane. But the stress may also have fallen particularly on some other structure of the joint, thus producing a complicated sprain. Immediately after the accident, with the joint full of fluid, an estimate of the exact nature and extent of the injury may be difficult, but the importance of its deter-

mination is manifest. At first the question of fracture must be settled by radiogram. Local tenderness will reveal where the capsule and the superficial parts of the bone ends are injured. Hyper-mobility in certain directions will result from rupture of main ligaments, intra- as well as extra-articular. The degree and extent of any restriction of movement will be decided by the amount of effusion, and by any mechanical blocking which may exist, as from displacement of bone fragment, fibro-cartilage, or loose body. The possibilities of other than purely ligamentous or synovial damage vary very much with the joint injured. In the knee, violence greater than that producing the common type of sprain of the internal lateral ligament may cause tearing or dislocation of the inner semilunar cartilage, and rupture of the crucial ligaments. Synovitis can occur from direct blows on the knee, and from indirect violence sustained in various ways. Condyles and tuberosities may be fissured or split off in any degree, or the central tibial spine fractured. The extent of damage sustained by the articular cartilage is impossible to detect in the early stages. If the knee has been previously affected by chronic arthritis, or been liable to attacks of derangement, the effusion may be due to nipping and contusion of old hypertrophied fringes or sub-patellar fat pads, to fracture of an osteophyte, or to the wrench accompanying a sudden blocking of movement by a loose bony body or a mobile semilunar cartilage. If old adhesions exist a knee may suddenly swell as the result of their rupture. When the quadriceps muscle is wasted, particularly the vastus internus, effusion is liable to occur in the knee on the most trivial injury. In the elbow joint, particularly in children, traumatic synovitis is frequently due to some degree of fracture into the joint, and this must not be overlooked. In the wrist the possibility of fracture of a carpal bone, or of the styloid processes of the ulna and radius, is to be remembered. In finger joints the lateral angle of the base of a phalanx may be torn away in a wrench injury. In the ankle a fracture of one or other malleolus, or of the posterior part of the lower end of tibia, causing a fissure extending into the joint, is often misdiagnosed as a simple sprain.

Cases occur in which the initial traumatic symptoms are slight and almost negligible, but chronic synovitis characterised by various degrees of synovial thickening and effusion gradually supervenes. This liability is greater if local nutrition has been neglected and muscular wasting and the formation of adhesions not prevented. In such cases the possibility of the secondary incidence of some infective process, such as tubercle in children and rheumatoid conditions in adults, causes anxiety, and the

differential diagnosis may be difficult. If the condition remains purely traumatic throughout, it may depend on original damage of the bone ends or articular cartilage, which might only reveal itself later by the presence of loose bodies formed from exfoliating cartilage, or, particularly in the elbow and knee joints, by the process of osteochondritis dessicans. While in some cases infective synovitis of the rheumatoid type may be incited by injury, in others the more slowly developing hypertrophic (osteoarthritic) type of chronic arthritis may occur, as seen in the hip, knee, elbow, and shoulder. In these it is difficult to say if an infective element exists in addition to the traumatic. Probably in most cases it does not, and the slow degeneration is due to some seemingly trivial damage of a bone edge or cartilage surface which could not be detected or gave little concern at the time of injury, thus the arthritis remaining purely traumatic throughout.

The prognosis of a case of traumatic synovitis must depend largely on the exact injury lying behind the effusion. Treatment will proceed along the usual lines for acute injuries. Mechanical obstruction to movement is dealt with by manipulation or surgical means. Massage and mobilisation may precede any such measure, either to assist diagnosis of the basic injury or in preparation for other treatment. The first indication is to get rid of the effusion, and then to institute active movement in so far as it is painless. If any fracture exist, the question of weight-bearing must be decided along the lines previously indicated. Should it be thought that injury of the articular cartilage has occurred, its slower healing may necessitate the use of appliances to restrict movement or relieve weight; this condition may not, however, be detected until a few weeks after the injury, when continued pain and increasing limitation of movement, in spite of active mobilisation treatment, instead of the steady progress which might be expected after a sprain, would raise suspicions of its existence (*vide* article on Bruising of Articular Cartilage).

Muscles and Tendons

Pathology and treatment.—Strain and laceration of muscles and tendons, which constitute a large class of acute injuries, are somewhat analogous to sprains of joints, and result from voluntary over-effort, from direct laceration, and from sudden unexpected stress—when the muscle is caught unready for the sudden demand made upon it. Local pain and tenderness occurs, which in the early stages is increased by active contraction or passive over-stretching. Pain is also felt at night,

near the point of attachment of the injured muscle, on account of the surrounding muscles relaxing and going off guard. The contractile power of the muscle is soon lost and wasting occurs rapidly. If the tear is superficial a sulcus is present in the muscle substance, but usually the muscle belly is not torn across completely, the gap being eventually bridged by fibrous and not by muscle tissue. Any degree of hæmorrhagic extravasation results. In the later stages muscle tears are often tediously painful, possibly from the adhesions due to the scarring. Rupture can occur anywhere in the course of a muscle, and is commonly met with in the calf muscles, biceps (arm and leg), rectus femoris, adductors of the thigh, tibialis posticus, deltoid, and spinal extensors. *Tendons* are more liable to rupture at their bony insertions; *e.g.* the long head of the biceps from the glenoid tubercle, and the extensors and flexors of the fingers from the base of the terminal phalanx. The ligamentum patellæ is less frequently torn than the quadriceps at its insertion into the patella. The Achilles tendon usually ruptures at its narrowest part, but occasionally avulses a flake from the os calcis at its insertion. The extensor tendon of the terminal phalanx of the thumb may rupture spontaneously at the level of the wrist joint about ten days after the occurrence of a Colles' fracture; and a similar spontaneous rupture of one or more extensor tendons of the fingers may occur in association with rheumatoid arthritis of the wrist joint. Effusion may occur about those tendons which are enclosed in synovial sheaths. Pain and tenderness are occasionally noticed at a point in the sheath some distance from the site of rupture, as in the palm after a separation of the long flexor tendon from the terminal phalanx; this is due to the tension exerted on the proximal end of the sheath by the retracted tendon. In operations upon tendons the strength of the repair is greater in proportion as the integrity of the sheath is preserved.

The immediate *treatment* of acute injuries of the *muscle* substance is to check effusion and aid its absorption, and to keep the muscle and limb in activity. Alternately the whole limb is stroked and the local condition kneaded. Early passive movements in relaxation, within the inner range, will help to prevent adhesions. Early active contraction and relaxation movements of the torn muscle may at first be possible only through a small range, but a continually increasing range should be obtained as rapidly as possible, with care to avoid detrimental strain. Interrupted and graduated faradic contraction is frequently used in the treatment of muscle tears, having been found to be more rapid and satisfactory in its results than

massage and mobilisation alone. It prevents early wasting by securing active and isolated contraction of the damaged muscle at such time as the active movement of the muscle or its associated joint would be impossible or injudicious. The muscle is "exercised" without calling its synergists into action. By virtue of its localised application it restores a very wasted muscle more rapidly than voluntary contraction could. The electrical method is also very useful in the later stages if painful adhesions have formed. A method long used in the treatment of muscle tears is that of strapping the limb circumferentially for a few inches beyond and over the tear, and then permitting full activity. The strapping is applied with the limb fully relaxed; it does not actually compress the limb, and certainly must not restrict the circulation, but merely renders the skin inextensible at the injured site. It partly restrains the torn ends of the muscle, and the muscular contraction against the now inelastic skin favours the circulation and the absorption of effusion. The strapping is reapplied when loose, and its use continued until the cure is complete; it does not hinder the application of massage. The patient is enjoined to get about from the first if at all possible, or at most within a day or two, and to resume his athletic activities.

Tennis leg is a rupture of some of the muscular or tendinous structures in the calf. A sulcus is present unless the injury is in the deeper portions of the muscle. Probably the rupture is never in the plantaris muscle or tendon. Strapping is applied after the limb has been elevated for five minutes, and immediately full use is begun, with care to bring the heel to the ground in every step. The leg is restrapped as the plaster loosens, and massage applied over the plaster. Stairs can be mounted in a few days.

Rider's sprain is an injury of the adductor muscles of the thigh, being anything from a slight strain to complete rupture; usually it involves the adductor longus muscle alone, but sometimes includes the other adductors. The rupture occurs at the origin or in the belly of the muscle. Pain, swelling, sulcus, and ecchymosis result in proportion to the severity of the injury; the pain may be referred to the perineum. The part is kneaded until the swelling is diminished sufficiently to render the application of the strapping possible, which is in about three days. This injury is that in which treatment by graduated faradic contraction has its most striking results; it can be carried out coincidently with the massage and the strapping. The patient rides after a few days, but quietly, and must not jump. The strapping is renewed when loose, and in a few days

later jumping is possible. If the cure is incomplete, the trouble is liable to recur each season on slight causes. These chronic cases show much atrophy and contracture of the adductors, which are painful when stretched, and manipulation under anæsthetic, followed by graduated exercises, may be required.

Sprained back.—Most traumatic disabilities of the spine are of bony rather than muscular origin (*vide* article—Painful Conditions of the Spine). Rupture of the extensor muscles of the spine occurs mostly in the lumbar and sacral regions. Pain is usually severe, and is liable to become chronic, when it may perhaps foster "functional" symptoms. The diagnosis is based on the site of tenderness, on the type and direction of the movements causing pain, and on the negative skiagraphic evidence. Firm kneading and full active movements should be given from the first. Manipulation under anæsthetic may be required later, to break down adhesions.

Many similar muscle tears result from athletic activities, particularly in the muscles already mentioned. In most of these treatment by open operation has no field, as muscle substance does not readily lend itself to suture except where it is becoming tendinous. A separation of the quadriceps from the patella is, however, often sutured. Short of the exceptional cases requiring open operation, the treatment in the acute stage of all these injuries of muscle substance is summed up in "rub, strap, and use."

Tennis elbow is characterised by radiating pain in the outer or extensor aspect of the upper part of the forearm, felt on forced extension of the elbow when the hand is in grip—as in taking a back-handed shot. There is localised tenderness immediately below the external epicondyle or over the posterior aspect of the radio-humeral joint, or in both. Occasionally there is a little effusion or thickening at the site of tenderness. The disability is liable to be protracted and tedious, but most cases recover spontaneously on abstention from the particular exercise causing the pain. Usually the x-rays are quite negative. The common view of its pathology is that the lesion is a tear of the extensor muscles at their origin from the external condyle, with the subsequent formation of adhesions or of localised periostitis, but there seem to be several distinct conditions which can account for the clinical symptoms. In four chronic cases operated upon by the writer, on account of failure of the usual treatment, two revealed a small bursa immediately below the epicondyle, between the superficial and deep extensor origins, and tending to herniate through the superficial aponeurosis; one showed a congested synovial fringe at the back of the radio-

humeral joint and small patches of erosion of the articular cartilage in the greater sigmoid fossa of the ulna; and the fourth case showed nothing abnormal. In the third case, which was clinically quite typical, and which occurred in a very active tennis player, there was no clinical or radiographic signs of arthritis of the elbow joint, although the patient did complain of pain and creaking in the shoulder. The usual treatment is by massage, graduated faradic contraction, strapping of the upper four inches of the forearm—but without restricting flexion of the elbow, active exercise insufficient to produce the pain, and correction of faulty methods of play. In some cases massage makes the pain worse. These measures are uncertain in their result, and, as has been said, most cases recover in the absence of over-activity. A few cases definitely appear to be cured by manipulation, and in these the pain must have been due to adhesions resulting from a ligamentous sprain, a muscular strain, or from a bursitis in which the acute inflammation had already subsided. Osgood's investigation showed that the epicondylar bursa is present in 50 per cent. of normal arms. The cases mentioned above which were submitted to open operation had been manipulated previously by bone-setters but without benefit. Removal of the bursa and of the synovial fringe, and the mere exploration in the negative case, were sufficient to effect a cure.

Post-operative treatment of tendons.—Open operation is done for resuture after injury, tenotomy, tendon lengthening, and transplantation. Tendons which separate widely after rupture should be sutured if practicable. Suture of the long flexor tendons after separation from the distal phalanx is unavailing, as the scar and the adhesions incite a gradually increasing flexion deformity which renders the finger useless. Ruptured extensor tendons of the fingers, producing "mallet finger" or "dropped top" deformity, usually unite completely if the finger is uninterruptedly kept on a splint for three weeks with the inter-phalangeal joints fully extended and the metacarpo-phalangeal joint flexed. Suture of the Achilles tendon is advisable after spontaneous rupture, as there usually results an irregular tear with frayed ends, which, if treated otherwise than by operation, is liable to a weak and painful union, prone to stretch later. A rupture of the ligamentum patellæ is always sutured. The long head of the biceps should be sewn to the coracoid process, as its original site is difficult of access and the operative compromise leaves nothing to be desired in the eventual function of the biceps. After tenotomy the extensor tendons on the dorsum of the foot heal without trouble, the only

difficulty being to maintain their increased length; so also the peronei tendons. The Achilles tendon heals well after subcutaneous lengthening, and also after lengthening by open operation if the sheath be preserved, except in spastic paralysis and sometimes in flaccid paralysis of the gastrocnemius, after which, in the absence of due care, the tendon is liable to heal over-lengthened and to be weak, with considerable risk of further stretching occurring subsequently. When the cut ends of a tendon are held in reasonable apposition by posture of the limb or by suture, healing proceeds rapidly, and the union is strong in three weeks. Mobilisation treatment must begin as soon as possible after the operation. Passive movements in relaxation can be given within that inner part of the range of action which the retentive splint allows; or it may be possible to omit the splint during treatment if precautions against over-stretching are taken. Active movements within this restricted range ought to be started within a few days at most after the operation, and the sooner the better; this applies particularly to suture of the tendons about the wrist after incised wounds. The early movements are vital in preventing adhesions of the tendons to their sheaths. The amplitude should be increased daily, with the object of obtaining full range in three weeks; but no great strain, such as would be entailed in walking, is permitted for another three weeks. The whole limb should be treated, to preserve the circulation, the strength of the muscles, and the movements of the most distant joints. After transplantation of tendons a literal re-education of co-ordinated movements will proceed coincidently with mobilisation of the tendons.

Traumatic teno-synovitis. Chronic strain.—Effusion into tendon sheaths may account for part of the swelling associated with a sprain of a neighbouring joint, in which the sheath may be lacerated and the tendon strained. Chronic strain is met with when tendons and their muscles are being over-worked and over-stretched in the effort to prevent the gradual occurrence of sprain and deformity; examples are found in the tibialis posticus in commencing "weak ankle" and flat foot, in the peronei in "turned ankle," in the extensor tendons in excessive use of the hand and fingers. The latter condition comprises several occupational disabilities, as found in pianists, typists, and writers. Chronic strain is determined by the degree and constancy of the effort, but is much influenced by the general health of the patient; when of some duration it is prone to foster neurosis. Pain, cramp, swelling and tenderness occur in the over-worked muscles, which become wasted and flabby; the tendons also are sensitive, and effusion takes place into the

sheaths. In the foot an improper walk, with restricted motion of all the joints, is unconsciously developed in the effort to avoid active use of the affected muscles and tendons, and thus spare pain, with the result that adhesions form in the sheaths and about the ligaments of the immobilised joints, this adding a further element to the painful disability. The treatment consists of relief from the incessancy of the initial strain, shampooing, stroking and kneading of the whole limb to aid circulation, local kneading to reduce the effusion, and re-education of the over-stretched and wasted muscles. In the occupational disorders of the arm less specialised exercises should be done, necessitating the use of different muscle groups and involving larger and coarser movements; these must alternate with those entailed in the vocational work, which itself should be limited to unexcessive amounts. The associated joints should be mobilised, particularly in the direction in which the affected tendons act, by passive and voluntary movements in the early stages, assisted by preliminary forced movement under anæsthetic if the condition is of old standing and the fixity great. Support by strapping and by building up the shoes will assist in relieving strain when ordinary use of the part is again permitted.

SECONDARY PELVIC CONTRACTION

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FROM time to time obstructed labour is encountered in multigravidæ whose previous history of confinements has been without abnormal incident. This class of case is of great obstetric importance, and occasionally presents features of considerable anatomical interest. From an ante-natal point of view the record of preceding spontaneous deliveries in an individual patient is inevitably disarming, and external measurements may fail to indicate the true state of affairs. All too often the serious nature of the problem is not recognised until a very late stage of labour has arrived, when craniotomy or Cæsarean section in an infected field afford the only solution. By this time the patient is commonly exhausted, and the attendant risks of either course are grave.

The causes of obstruction in these multigravidæ have been variously attributed to misdirection, inertia, and disproportion due to the size of the fœtus exceeding that of its predecessors. Undoubtedly these factors play a part in a large number of cases. The pendulous abdomen resulting from a series of confinements is associated with anteversion of the pregnant uterus, and in labour the expulsive forces may tend to be directed towards the sacral promontory rather than the pelvic cavity. The lax abdominal walls and enfeebled uterine musculature of a debilitated multipara are unable to cope with any additional mechanical obstacles and necessarily accentuate the difficulties, although they cannot be regarded as a primary cause of obstruction. The increasing size of successive fœtuses has been advanced as an explanation of this incidence of obstructed labour in multigravidæ; but we cannot accept this as a general rule, although it may obviously represent the whole source of trouble in a given individual.

The further possible factor to which we would refer is an actual decrease in the size of the pelvic brim *resulting* directly or indirectly from antecedent confinements, which may themselves have appeared uneventful. Clinical experience and measurements in certain cases have indicated this possibility, which is indeed suggested by mechanical considerations. The

unhappy termination of the case under review has afforded material for more exact observation and the confirmation of clinical impressions by anatomical determinations. Incidentally it also serves to emphasise the extreme risk of the repulsive procedure of craniotomy to which we are occasionally forced.

A woman, 40 years of age, had had six previous confinements at full term. In each case labour had been spontaneous, of comparatively short duration, and without untoward incident. All six children were alive, and the youngest two had weighed 7½ and 7¼ pounds respectively at birth (earlier weights were not recorded). Her external pelvic measurements were not abnormal. Her abdominal walls were lax, and she had been advised to wear a belt during pregnancy.

On the present occasion labour started at term. The duration of the first stage is not recorded; but she had been in the second stage for three hours when she was transferred to hospital. She arrived in a somewhat exhausted condition. The vertex was presenting, but freely movable above the pelvic brim. The fœtal head could not be pushed into the pelvis, and the diagonal conjugate was noted to be small (4¼ inches). However, as the child was alive, an attempt was made to deliver by means of axis traction forceps. This failed completely, and craniotomy was performed. Unfortunately, rupture of the membranes some hours earlier and attempts at forceps delivery were held to contraindicate Cæsarean section, on account of potential sepsis. The weight of the child was judged to be about 7 pounds, the conditions of craniotomy precluding exact estimation. The patient died a few hours later.

Pelvic measurements.—On post-mortem examination the measurements at the pelvic inlet were found to be as follows :— transverse diameter 5 inches; oblique diameter 4½ inches; antero-postero diameter or true conjugate 3½ inches (normal 4¼).

This pelvic flattening was of an unusual character in that the whole of the upper part of the sacrum was displaced forwards in relation to the iliac bones, thus rendering very prominent the sacral margins of the sacro-iliac joints. As a compensatory factor the lumbar lordosis was increased to a marked degree, leading to undue prominence of the inter-vertebral disc between the last lumbar vertebra and the sacrum. At a subsequent examination the lumbo-sacral angle was found to measure 95° (normal 130°).

The sacro-iliac joints.—The sacro-iliac joints on each side were movable but not to the degree usually found in pregnant women.

At a previous examination of over 200 normal joints [1] obtained chiefly from post-mortem subjects, it was found that

in the young adult female antero-posterior rotation backwards and forwards of the sacrum on the ileum is possible through an angle of from 10 to 12°.

In addition to this rotation occurring around an axis passing through the lower extremity of the joint, very slight forward and downward movement of the sacrum as a whole could also be elicited. This forward movement is usually combined with the previous one and occurs around an axis which is situated well below the joint, so that the upper part of the sacrum moves forward and backward to a greater extent than the lower.

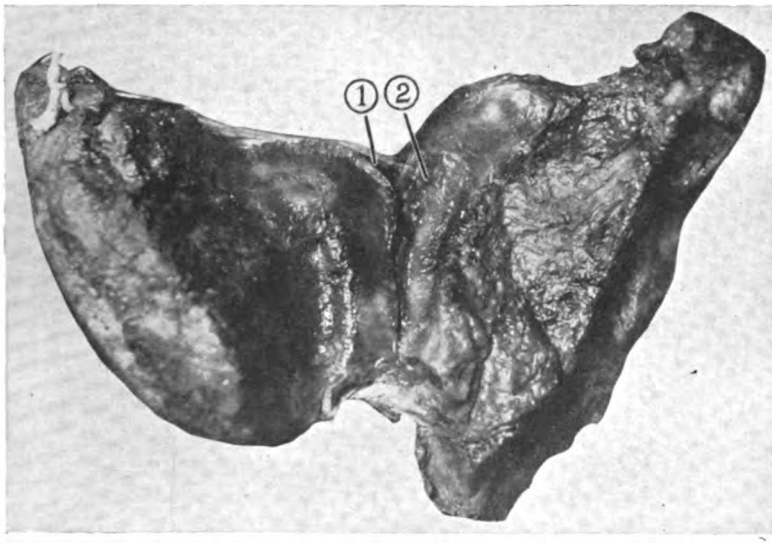

FIG. 1.

The Sacro-iliac joint of a female subject opened from behind, showing a well-marked sacral crest (1) and corresponding depression on the iliac bone (2).

During pregnancy a well-marked increase occurs in the range of both forms of movement. This increase takes place gradually, and at the fourth month is easily recognisable. During the seventh, eighth, and ninth months the mobility increases rather more rapidly, and at term rotation may be produced through an angle of 25° (2½ times the normal). Sixteen joints taken from pregnant women at term were examined; and all of them showed that, in addition to the increased range of normal rotatory movement, the ligaments and capsule were so lax that the sacrum could be pushed bodily downwards and forwards into the pelvis for some distance. The anterior margin of the joint surfaces could also be separated from each other in a horizontal direction for a distance of ¼″ on each side.

After parturition the joint is slow in returning to its original state. Thus at the eighth week the ligaments are still relaxed and the joint is still unduly movable. It is not until the third or fourth month that stability is completely regained.

In the case under discussion the range of rotation was only 15°; and forward movement of the sacrum as a whole could not be obtained.

On opening the joint a well-marked intra-articular crest was to be seen. This crest of bone, sometimes a tubercle, is a constant feature in both male and female joints. It varies

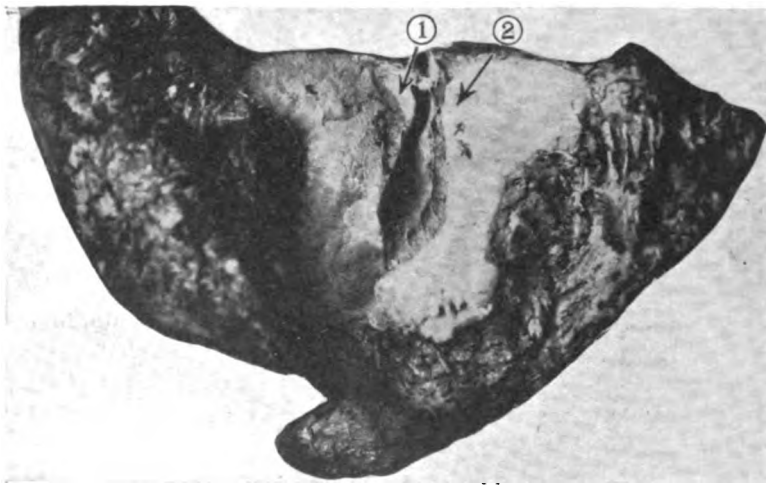

FIG. 2.

The Sacro-iliac joint from the case described, opened from behind. The sacral tubercle (1) is seen displaced forwards to the front of the joint; (2) is the depression, to which it should be fitting.

considerably in size and is situated at the junction of the ascending and horizontal limbs, towards the anterior margin of the joint. It is covered with articular cartilage, and usually fits into a corresponding depression in the articular surface of the ileum (see Fig. 1). In this case the crest was abnormal in that it was displaced downwards and forwards from its socket, and was lying in front of the anterior margin of the iliac articular surface, against which it was closely impacted (see Fig. 2). After opening the joint it was possible by using some force to disimpact the two bones. It was found that in order to produce simple displacement of the sacral crest from its socket forwards rotation of the sacrum was necessary. On rotating the sacrum backwards it returned quite smoothly to its original position.

If now the sacrum was first depressed and then moved bodily forwards on the ileum, on rotating the upper part of the sacrum backwards slightly, the displaced crest became impacted against the anterior edge of the iliac articular surface and the original deformity was reproduced.

In submitting an explanation of the manner in which the deformity was produced, it must be assumed that the patient rose too soon after her previous confinement, at a time when the ligaments of her pelvic joints were in a softened and stretched, perhaps unduly stretched, condition. In consequence she was unable to support the weight of the trunk efficiently on her pelvis, the whole sacrum sagging in a downward and forward direction to the limits of the stretched posterior sacro-iliac ligaments. As it did so it carried with it the intra-articular sacral crest, which passed into a position in front of the anterior margin of the articular surface of the ileum. In an effort to restore the line of the centre of gravity, the patient now accentuated her lumbar lordosis by increasing the backward inclination of the lower lumbar vertebræ, and by rotating the upper part of the sacrum backwards. In this way the displaced sacral crest became locked against the anterior margin of the iliac articular surface. The ligaments of the joint now shortened up as involution proceeded, and contracted down upon the joint in its abnormal position. Subsequently, at the next pregnancy, movement at the joint was found to be limited in degree, and the pelvis flattened.

It will be noticed that the term subluxation has been purposely avoided in this description. Although the underlying mechanism and predisposing causes of partial subluxation are probably identical with those of the displacement just described, yet it differs in that an antecedent traumatic factor is usually present in the former, whereas in the latter it is absent and the deformity occurs more gradually, and often painlessly.

The movement at the *lumbo-sacral* articulation was remarkably free; flexion and extension occurring through an angle of 45°. This condition of increased mobility is probably compensatory in origin and resembles the condition present in a large proportion of adult males of over fifty years of age. In these cases diminished mobility and ankylosis of the sacro-iliac joints is very common.

Craniotomy is recorded as having been performed on fourteen occasions at Guy's during the years 1923, 1924, 1925. Six of the cases were primigravidæ, and one was a case in which the

single previous child had been delivered with difficulty and weighed only four pounds at birth. In two of the multigravidæ the operation had been performed for reasons definitely other than dystocia. These nine cases obviously do not concern the present issue.

Of the remaining five (multigravidæ) there were two in which other factors arose :

1. Eleven previous confinements—seven alive, four still born (breech deliveries). In this case the fœtus subject to craniotomy was large, its estimated weight being 9 lb. 10 oz.

2. Six previous confinements. The last two children had weighed 11 pounds and 10¼ pounds respectively at birth. History of uterine inertia. In this case there was a persistent occipito-posterior position of the head, and the child weighed 10¼ pounds, in addition to the cranial contents removed in the course of craniotomy.

Three cases appear to indicate acquired pelvic contraction :

1. Nine previous confinements; all spontaneous deliveries; all children born alive.

In this case the presentation and the position of the fœtus were normal, and there were good uterine contractions; but the head was obstructed at the pelvic brim, and a small diagonal conjugate was noted. Forceps delivery failed completely, and craniotomy was performed. The child was of average size.

2. Two previous confinements; both spontaneous deliveries; both children alive. The duration of labour in the second case had been four hours only.

Presentation and position normal. Forceps delivery failed; craniotomy performed. Weight of child 7 lb. 10 oz.

3. Five previous confinements; the last three deliveries had been spontaneous.

Presentation and position normal. Forceps delivery failed; craniotomy performed. Small conjugate noted.

It is recognised that clinical evidence in this direction can only be suggestive, even were the records more complete. For this reason we have not adduced the far more numerous cases in which a difficult and possibly dangerous "high" forceps operation has sufficed to overcome lesser degrees of pelvic contraction; although, in the light of our present observations, we may reasonably assume that some of these have also been acquired in the course of previous obstetric events.

It may be that individuals seriously affected by the condition under review are few and far between. Nevertheless the practical issues arising from its recognition are of the utmost

moment. Craniotomy is a brutally inartistic and dangerous operation to be avoided at all costs; the high forceps operation is very little better. Theoretically there are no considerable difficulties involved in diagnosis and obstetric treatment; practically, the problem is not quite so simple as it would appear, and demands consideration at four stages.

Prevention.—It has been shown that the relaxed pelvic joints involute very slowly after labour, particularly in cases accompanied by uterine subinvolution. This indicates an extension of the lying-in period beyond the nine or ten days traditionally adopted by the working-class mother, a course of massage and graduated exercises, and a gradual return to her household duties. It further indicates a limitation of pregnancies in the case of women who are not fitted to withstand the strain of confinements at frequently recurring intervals. Apart from the major degrees of deformity that may lead to obstetric complications, there is little doubt that the far more numerous pelvic displacements and readjustments of lesser degree are largely responsible for the backache and lassitude of which the overburdened multipara so commonly complains. But it is merely futile to advocate these obvious measures under present-day conditions.

Ante-natal diagnosis.—It is inevitable that these cases of acquired pelvic contraction should tend to escape recognition at the ante-natal clinic. They are of infrequent occurrence, the previous obstetric history is usually good, the external pelvic measurements are not considerably affected, and the fact that the fœtal head is not engaged towards the end of pregnancy in a multipara does not excite comment. To measure the diagonal conjugate by a somewhat painful vaginal examination as a routine, in the case of every woman who presents herself, is impracticable; and to estimate with certainty the relative size of fœtal head and pelvic brim in every case without (or even with) an anæsthetic is a practical impossibility. Midwifery is not an exact science.

Diagnosis and treatment early in labour.—This is essentially the time to recognise this class of case. Provided the condition is borne in mind and regarded as a serious possibility, a previous history of spontaneous deliveries will not blind the eyes of the medical attendant to the fact that the fœtal head is not engaging and will not engage in the pelvic brim. Vaginal examinations and vain attempts to deliver by forceps may then be avoided, and the field left clear for the performance of Cæsarean section without undue delay.

Treatment at a late stage.—When the obstruction is not

recognised until the membranes have been ruptured for some length of time and the patient's resources are already taxed, the problem of treatment resolves itself into a question of relative risk as between craniotomy and Cæsarean section in a potentially infected field. It is beyond our present purpose to express any definite opinion on this point beyond noting that the dangers of the latter have been considerably overrated, and that the modern obstetrician, fortunately or unfortunately, has not the same facilities for acquiring proficiency in the use of the cranioclast and cephalotribe as were granted to his predecessors.

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CASES FROM THE EAR AND THROAT DEPARTMENT

I. A CASE OF PNEUMOLITH SPONTANEOUSLY EXPELLED BY COUGHING

By T. G. BENJAMIN and W. M. MOLLISON, M.A.

R. O., aged 53, attended the Throat Department on May 4, 1926. He stated that for a considerable time he had been suffering from general malaise and that for a month he had been receiving medical treatment for a cold, abdominal pain and a choking feeling in the throat. He had had a persistent cough with fairly copious expectoration of white mucus. The feeling of obstruction in the throat was more pronounced at night, interfering with sleep, and on more than one occasion causing some respiratory distress. Two days before attendance he had expectorated a large quantity of green phlegm, in which he had found the hard object which he brought with him for inspection. The patient looked ill and pale, his appetite was poor, and for the past month he had been living on a very light fluid diet, as he had experienced some pain and difficulty in swallowing solids. Examination of the upper respiratory tract revealed no abnormality. At his subsequent attendance a week later the patient reported great improvement; the throat symptoms had disappeared, the cough was much less, and appetite had been regained.

There can be little doubt that this was a case of spontaneous expectoration of a foreign body from the lower air passages, and interest centres round the origin of that body: it is suggested that this is a case of spontaneous expulsion of a pneumolith.

The specimen was irregular in shape, a good deal longer than broad; it showed various small projections, such as are to be seen in a rabbit's vertebra. It was very hard and was dark grey in colour; it measured 2 cms. in length and 1 cm. across.

Professor T. J. Evans, M.A., of the Biological Department kindly examined the specimen and reported as follows:—"The outer soft layers are almost entirely composed of bacteria of many kinds, among which a diplococcus and a streptococcus are most numerous; there are also bacilli, strepto-bacilli and a streptothrix. Squamous cells are very scarce, but here and there are

plant fibres and woody nodules like those of a pear. The bacteria are embedded in a kind of caseous (rather than mucous) material. In the deeper layers the matrix is harder and contains a fair amount of inorganic matter soluble in dilute hydrochloric acid with effervescence, and therefore possibly carbonate. There is no bony substance, and I feel sure the whole grew in the patient."

Mr. H. C. Bell in the Chemical Department kindly examined the specimen also; he found the mass to consist chiefly of inorganic matter, mainly calcium phosphate; a trace of carbonate was present with a minute trace of some other metal; the organic residue was nitrogenous and minute in amount.

Dr. N. Mutch saw the patient: he found some dullness at the roots of the lungs and poor excursion of the chest. His conclusion was that the man had some emphysema with old fibrosis at the roots.

The following is Dr. Lindsay Locke's radiological report :— Median opacity normal. Diaphragm moves evenly, but not freely. Costo-phrenic angles clear. Some infiltrations of both sides extending from the roots with an old dense calcified patch in each lung. No evidence of cavitation.

It is true that cases are recorded of foreign bodies in the trachea and bronchi in which no history of inhalation can be obtained. An adult may inhale or swallow a foreign body during sleep or when intoxicated. Also when inhalation has taken place, it may be some weeks before symptoms arise; even if the body is free to move, attacks of dyspnœa may be slight and infrequent.

In this case there was no history of a foreign body, and the biological and chemical examinations suggest its formation in the lung. Its chemical composition corresponds roughly in nature and proportion to the lime salts deposited in necrosed tissues when they become calcified. It is therefore possible that the foreign body was a calcified tuberculous nodule or a calcified mass from a lymph gland, which penetrated the wall of a bronchus and was expelled by coughing.

Pneumoliths are recorded as having passed through the wall of a bronchus and thus presented themselves as foreign bodies.

There is in the museum at Guy's a specimen showing a calcareous mass from a gland lying in a bronchus, with the hole in the wall leading to the gland whence the mass had come.[1]

Burger [2] published a most interesting case of extraction of a

pneumolith from the left bronchus by means of the bronchoscope. The patient was a lady of 48, and had had symptoms comparable to those of our patient for six months. Bronchoscopy showed a pink mass projecting into the lumen of the left bronchus, and in the midst of this mass a white spot; this was detached and removed. It was at first thought to be a foreign body, but further examination showed it to consist of carbonate of lime for the most part.

Burger quotes two cases from the literature, one of Killian's, in which a woman of 65 coughed up a pneumolith, and the other Chevalier Jackson's, in which some friable stones were removed through a bronchoscope. He adds, however, that these were probably broncholiths rather than pneumoliths.

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II. TWO CASES OF APPARENT CURE BY OPERATION OF MALIGNANT GROWTH OF ANTRUM AND ETHMOID

By S. L. A. CLARKE and W. M. MOLLISON, M.A.

The interest of the following two cases lies in the apparent cure of malignant disease of the ethmoid and antrum respectively by operation. In the first case there has been no recurrence of a sarcoma of the ethmoid after eleven years, and in the second no recurrence of a carcinoma of the antrum after thirteen years.

Case 1.—Nellie R., aged 19, was admitted to Ruth Ward in December 1914, on account of severe epistaxis, which had been persistent for three weeks. The patient also suffered from headaches; she had noticed a tender swelling at the inner upper part of the right orbit and had suffered from right-sided nasal obstruction with a discharge from that side of the nose.

X-ray examination of the skull showed that the right ethmoidal region was opaque.

Operation was performed through Moure's incision; growth was found in all the ethmoidal cells, invading the maxillary antrum; it was possible, however, to make a thorough removal.

Microscopical examination by Dr. G. W. Nicholson showed a round-celled growth, which in his opinion was a neuroblastoma.

The patient made a good recovery, and during convalescence

was given some exposures to x-rays (not, of course, "deep" x-rays).

She attended again at hospital about six months later, but was then lost sight of. In June 1926 the patient again presented herself in the Out-Patient Department, complaining of a swelling in the inner and upper angle of the right orbit, tender on pressure. This swelling was not unnaturally considered to be a recurrence of the former growth, and the patient was admitted for operation. It had been present about a month, together with some nasal discharge and obstruction.

Operation through the previous incision was performed; fortunately the swelling was found to be a collection of pus in the old operation area, and there was no sign of growth.

St. Clair Thomson, in the 1926 edition of his *Disease of the Nose and Throat*, writing on the question of malignant disease about the nose, states that "the prognosis is more favourable when the growth is near the floor of the nose, and becomes less so as it approaches the ethmoid region. . . . Still, the outlook for malignant disease of the nose is not so gloomy as might be expected, and is less so than it was some years ago. . . . A recurrence may take place after a clear interval of as much as seven years."

Dr. Nicholson has re-examined the original specimen, and reports as follows:

"An alveolar small-round-celled new growth, which has completely replaced the mucous membrane. At first sight it resembles a sarcoma, but the centres of the alveoli are occupied by non-cellular granular matrix, around which the cells form 'rosettes.' The tumour thus appears to be a neuro-blastoma, which may have originated in the olfactory lobe."

Case 2.—Elizabeth C., aged 47, was operated on for carcinoma of the left maxillary antrum in 1913. The symptoms were characteristic of that disease; swelling of the face associated with pain and epiphora, nasal obstruction and epistaxis. Moure's incision was employed. The growth was found to originate apparently about the roof of the antrum, and, though it filled that cavity, it did not invade the floor, which was therefore spared while the anterior upper and inner walls were removed. On account of œdema of the lower eyelid following operation, the disfigurement was considerable for a time, but it disappeared; the scar is now scarcely visible and there is no disfigurement.

Some six months later enlarged glands appeared in the neck; these were removed, and on section one showed infiltration with carcinoma.

The patient used to report at intervals for a few years, and

then disappeared till July of this year, when she complained of some ear symptoms on the opposite side. There is no sign of recurrence of the growth, nor has the patient any symptoms in connection with the area of the previous operation; the scar of the gland operation is also good and supple.

The following is Dr. Nicholson's report on the specimen removed in this case:

"A cellular basal celled carcinoma with slight attempts at differentiation into irregular glandular tubules. The bone is extensively infiltrated. The tumour is hæmorrhagic and necrotic and does not differ from the general type of basal celled carcinoma of the air sinuses."

III. A CASE OF SUBDURAL ABSCESS FOLLOWING AN OPERATION ON THE MASTOID PROCESS. (RECOVERY.)

By H. W. A. POST and W. M. MOLLISON, M.A.

Mrs. M., aged 38, attended in the Out-Patient Department on April 21, 1926, complaining of pain in the left ear, tinnitus, vertigo and deafness. The patient had suffered from constant otorrhœa for many years on the left side, while occasional otorrhœa had occurred on the right side. For about a year deafness and tinnitus had increased on the left side, and for six months vertigo had been present, worse recently.

The patient was very giddy, tending to fall when she tried to stand, though not in one direction more than another. The eyes showed a fine rotatory nystagmus towards the right side; this was greatly increased by exerting pressure in the left external meatus: in other words, the "fistula symptom" was well marked. Her temperature was 97·8° and pulse was 80. Examination of the ears showed on the right side an old-standing posterior perforation with slight amount of pus: on the left was a polypus, blocking the meatus, and there was tenderness over the mastoid process at the tip, anterior margin and over Macewen's triangle.

The following day the left mastoid was opened: pus and cholesteatoma were found. The radical operation was completed, and an erosion of the external semicircular canal found; the dura mater of the middle fossa was exposed over the roof of the aditus and antrum, but looked normal. A meatal flap was cut, but no skin graft used.

Progress was normal till three days after operation; the temperature then rose to 102° F. and the pulse rate to 120; on the following day the patient vomited, became mildly delirious and complained of headache. There was tenderness

over the upper part of the wound. The reflexes were increased. Syringing the cavity with cool lotion produced contralateral nystagmus, showing that it was improbable that the symptoms were due to acute labyrinthitis.

No definite diagnosis was made, but in view of the meningeal symptoms, exploration of the cavity was carried out. There was no pus in the wound or the bony cavity; nor did the dura of the middle fossa show more redness than might be expected from its exposure at the previous operation. However, a small incision was made in it, and immediately foul turbid fluid escaped to the amount of 1 oz.: this pus apparently escaped from the subdural space and not from the brain. It was found to contain a Gram negative bacillus, *Bacillus xerosis*, and *Streptococcus brevis*.

Lumbar puncture showed the cerebro-spinal fluid clear and not under increased pressure; microscopically the fluid contained pus cells and Gram negative bacilli, while on culture it remained sterile.

The patient's condition was serious for some days after operation. Afterwards she had only a poor recollection of events between April 22 and May 5. She was restless and irritable, somewhat delirious, and complained of headache and pain in the lower limbs. These symptoms were relieved temporarily by lumbar puncture. The temperature was irregular, ranging from 99·5° to 102·5°.

Lumbar puncture was performed daily from April 26 to May 7, when the patient was convalescent; during that time the fluid was under increased pressure and contained pus cells and lymphocytes. Protein was present to the extent of 0·16 per cent. at first, but fell to ·017 per cent. at the last puncture; the cells were never more than 250 per c.mm. and fell to 25 per c.mm.

The abscess discharged freely at first and was dressed with hydrogen peroxide and eusol, a gauze drain being packed lightly into the sinus; healing eventually was satisfactory.

This case is of some interest, since subdural abscess is an uncommon complication of suppurative otitis, and there is a doubt as to whether the subdural infection did not occur at the first operation. It is possible for infection to be introduced under the dura by slipping of the gouge when the bone is being removed in the process of exposing the dura, the gouge actually piercing the dura. On one occasion this accident happened to one of us (W. M. M.) while operating on a case of acute mastoiditis; an abscess formed under the dura in three days, but after free drainage and lumbar punctures the patient made a good recovery.

When one considers the very large percentage of cases in

which the dura is exposed, one is struck with the minute number of cases of damage. Superficial damage may be enough to lower the resistance of the dura and allow the infection already in the wound to lead to an abscess in the subdural space. In this case there certainly was no actual tear made in the dura at the time of operation, but the whole mastoid cavity was very infected, and mere sponging could have damaged the exposed dura.

Again, damage to the dura may take place through small sharp pieces of bone which escape observation when they are separated, or they may not be separated but left pressing on the dura and thus gradually cause erosion. McKenzie has pointed out this danger, emphasising the importance of removing any such spicules.

The meningitis in this case was mild in type, so-called serous meningitis, and the treatment by repeated lumbar punctures quite satisfactory.

IV. A CASE OF LATERAL SINUS THROMBOSIS WITH ORGANISED CLOT: SIMPLE EXPOSURE. (RECOVERY.)

By H. W. A. POST.

Mrs. A., aged 46, attended the Aural Out-Patient Department on June 7, 1926, complaining of severe pain behind the right ear and vertical and occipital headache. The illness had begun, between two and three weeks before, with an attack of vomiting, which had lasted four days. Headache had accompanied the vomiting and had gradually become more and more severe. The patient had great difficulty in turning her head on account of stiffness of her neck; she had also suffered from neuralgic pains in the legs, dizziness on attempting to walk and some mistiness and disproportion of vision. During the forty-eight hours before admission the patient had had four rigors.

On examination the temperature was 102·8° and pulse 120; reflexes were normal, the fundi normal, and nystagmus was not observed.

A small amount of pus was present in the right meatus, and there was a posterior perforation in the membrane; the mastoid process showed no swelling nor redness of the skin; it was tender, however, especially at the posterior border and on percussion. There was no tenderness in the neck along the jugular sheath.

An operation was performed. The bone of the mastoid was

of ivory hardness: on reaching the antrum, pus escaped under considerable pressure; in the antrum and middle ear was a cholesteatoma, and in this were the remains of the malleus. The lateral sinus was exposed: its wall was deficient anteriorly, and the lumen seen to be occupied by organised clot, which was pale in colour and quite firm, and appearing to be partly fibrous tissue. On exposing the dura mater of the middle fossa, a considerable area of granulations was seen and found continuous with the affected area of the sinus. In view of the organisation of the clot in the lateral sinus, it was decided to take no further steps to deal with it, either by plugging the sinus above or ligaturing the jugular vein in the neck. The wound was left open with a rubber drain loosely filling the cavity. A lumbar puncture showed clear fluid with occasional lymphocytes and red blood cells; cultivation gave a growth of *Streptococcus brevis*; but it is probable that this was really due to contamination, in view of the patient's recovery without further surgical interference. Chemical examination showed 0·1 per cent. protein and some diminution of the sugar.

For three days the patient was very drowsy and complained of stiffness of the neck. Thereafter this sympton disappeared, and the pulse and temperature became normal; with the exception of occasional headaches and pains in the legs, the patient rapidly improved and made a complete recovery.

Two points may be noted in connection with this case: first, the absence of symptoms usually looked on as typical of lateral sinus thrombosis—rigors and spikes of temperature. The patient had not even felt "chilly," nor had she sweated; she had, however, that most important symptom, "stiffness of the neck." Her other symptoms, pain over the mastoid and in the occipital region, might have been due to the presence of pus under pressure in the bone or to the serous meningitis, which complicated the thrombosis.

The second point of interest was the organisation of the clot in the sinus; nature had made an attempt to deal with the sinus infection, and indeed had succeeded, though the continued presence of the infecting focus could not be disposed of; the mere evacuation of the pus sufficed to allow of recovery.

The occurrence of organisation of the clot with recovery is recognised; and indeed the sinus is occasionally found reduced to a fibrous cord, when the mastoid is opened months after the acute illness has passed. Such is not always the case; during the time taken in the organisation of the clot the patient may develop pyæmia with multiple abscesses in various parts of the body. Some years ago there was in one of the medical wards a child with bilateral otitis media; he was ill but showed no symptoms demanding operation on the mastoids; after some

weeks he developed symptoms of suppurative arthritis in the right knee. A surgeon opened the knee joint and found pus, and subsequently other abscesses were opened. The patient then developed signs of acute mastoiditis; operation showed pus in the mastoid and complete obliteration of the lateral sinus.

CARCINOMA MAMMÆ: THE RESULTS OF TREATMENT

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MATERIAL

THE investigation upon which this report is based was commenced in August 1925, and concerns the fate of 722 cases of carcinoma of the breast, admitted to the hospital during a period of thirteen years, beginning in August 1909 and ending in August 1922. To each case, apart from those who died in the hospital, a circular letter was sent requesting the patient to report upon her condition and, if possible, to attend at the hospital for examination. The great majority of the patients alive at the time of inquiry attended as requested, and most of those who did not attend were examined by their own doctors, who were kind enough to report their findings. According to the replies received, the cases were at first grouped as follows:

I. Cases traced to death	296
including (*a*) the operated cases—18	
(*b*) Operative deaths—23	
II. Survivors at the time of inquiry	153
III. Partially traced for a varying period, but not traced at the time of inquiry	52
IV. Untraced	221
Total . . .	722

The investigation was primarily undertaken to determine the results of operative treatment, and statistical information which has been incidentally obtained is given in the Appendix.

UNOPERATED CASES

In assessing the value of operative treatment in terms of longevity it is obviously essential to know the average duration of the disease when operation is withheld. In the 18 unoperated cases in this series the average length of life in 17 from the date of the appearance of the tumour to the date of death was found

to be 31 months. This period is somewhat shorter than that found by Lazarus-Barlow,[1] Greenwood [2] and others in larger series of cases, and it is generally accepted that a patient without operation may on an average be expected to survive about 36 months from the apparent onset of the disease.

Post-operative Deaths

Of 704 cases subjected to operation, 23 cases died within the hospital from causes directly attributable to the operation. The cause of death was as follows :

Septicæmia	7
Erysipelas	2
Pulmonary embolus . . .	3
Heart failure and shock . .	2
Unrecorded	9

The operative mortality was therefore 3·3 per cent.

Cases traced to Termination in Death

The date of death was ascertained in the case of 254 patients subjected to operation and discharged from the hospital alive. The average length of life of these cases is given below in relation to the nature and extent of the operation performed. For the purpose of classification the operative methods have been divided into the following groups :

Group I. Simple removal of the breast alone or the affected portion without the pectoral fascia or the axillary glands.

Group II. Removal of the breast with the pectoral fascia and some but not all of the axillary glands.

Group III. Radical removal of the breast with the sterno-chondral part of the pectoralis major, and the complete lymphatic contents of the axilla.

The average period of survival in months after operation according to the respective methods was as follows :

Group I.	Local or partial removal : 17 cases . . .	53 months
Group II.	Incomplete removal : 66 cases . . .	46 ,,
Group III.	Complete removal : 171 cases . . .	31 ,,
	Total 254 cases . . .	36 ,,

The average length of time which intervened in these cases between the patients' own observation of the tumour and the date of the operation was 8·8 months. The average duration of the disease was therefore 44·8 months, *i.e.* 8·8 months before and 36 months after operation.

It has already been pointed out that the average expectation of life in the absence of operation is about 36 months. It would appear, therefore, that in comparison the benefits of operation in relation to the prolongation of life were but slight in the 254 cases traced to death, and amounted in the average to a period of only 8·8 months.

It is important, however, that no general conclusion be drawn from this unfavourable comparison, which concerns only those patients who have succumbed to the disease and ignores those who have survived. The group of patients under discussion probably includes the worst and most advanced cases of the series. This assumption is supported by the average length of history before operation, for a patient who, to her own knowledge, has had a tumour of the breast for 8·8 months can hardly in most cases be considered as an early case.

The Nature of the Operation

On turning to the average period of survival shown above in the cases traced to termination, it is most striking to notice that those patients subjected to a partial or incomplete operation survived for a considerably longer period than those treated by more radical measures. It would appear, in fact, that the average period of survival is inversely proportional to the magnitude of the operation.

Assuming that the cases under discussion are late cases, these findings are to be anticipated, and a study of the recurrences and metastases after operation supports the view that the more advanced the growth the more likely is an extensive operation to be followed by rapid and fatal dissemination.

There can be little doubt that the cases subjected to local or partial operation were even more advanced than the average of the series traced to death, since the average length of history before operation was in the former 13 months and in the latter 8·8 months. None the less the average period of survival after the local or partial operation was 53 months as compared with the general average of 36 months.

The conclusion can hardly be escaped that in late cases, where there is but little possibility of completely eradicating the

disease, the less extensive the operation, the longer the survival of the patient.

The Operative Prognosis

It has already been pointed out that an operative prognosis based upon the cases known to have succumbed to the disease without reference to the survivors must necessarily be erroneous. Both groups must be considered together, and in dealing with the survivors certain difficulties arise.

It is evident that the term cure is impossible of application, since no patient, however long she may survive can be regarded as immune from the possibility of recurrence.

The only satisfactory method of stating the results of operative treatment is to arrange all the cases traced in groups according to the period they survived, irrespective of their condition at the time and their ultimate fate when known. This method has been followed. All cases in which there was no microscopic evidence of the disease at the time of operation or no confirmation by recurrence at a later date, have been excluded. In conformity with the usual practice of other writers on the subject, the three-year period of survival has been selected as the most suitable basis of classification.

Having excluded the unverified cases, there remains for consideration 338 verified cases, which are known to have survived for the periods shown below in Table I. In the great majority of these cases the operation performed was of the complete and radical type.

TABLE I.

The Survival Period of 338 Verified Cases.

	Total . .	338 cases.	Per cent.
Alive 3 years after operation	. . .	183	54·1
„ 4 „ „ „	. . .	127	37·6
„ 5 „ „ „	. . .	96	28·4
„ 6 „ „ „	. . .	72	21·0
„ 7 „ „ „	. . .	52	15·4
„ 8 „ „ „	. . .	47	13·9
„ 9 „ „ „	. . .	39	11·5
„ 10 or more „ „	. . .	21	6·2

It may be fairly stated on these findings that, with regard to the expectation of life, about one-half of the cases subjected to operation survive three years, and about one-quarter five years. In Table II are given the findings of other writers.

TABLE II.

To Show the Three- and Five-year Survival Percentages Collected from the Literature.

Author.	Date of paper.	Number of cases.	Three-year survival.	Five-year survival.
			Per cent.	Per cent.
Watson Cheyne [3]	1896	21	57·1	—
	1899	61	51·0	—
	1904	34	50·0	—
Warren [4]	1904	100	33·0	—
Steinthal [5]	1905	145	33·3	—
	1912	200	30·5	—
Halstead [6]	1907	191	38·3	30·89
Greenough [7]	1907	260	28·7	22·9
	1921	69	41·2	30·5
Meyer [8]	1907	80	35·8	30·0
Lindenberg [9]	1914	153	42·1	31·4
Schwartzkopf [10]	1912	321 (1895–1910)	29·4	21·0
		139 (1904–1911)	42·9	—
Judd and Sistrunk [11]	1914	266	44·7	39·8
Deaver and Mcfarlane [12]	1918	150	34·0	26·0
Hoffmann [13]	1920	315	36·3	28·5
Tichey [14]	1920	62	38·7	20·9
Iselin [15]	1920	102	44·1	26·4
Neher [16]	1920	57	37·5	21·0
Perthes [17]	1920	130	38·5	27·7
Forgue [18]	1921	285	40·3	—
Sistrunk [19]	1921	218	57·8	36·7
Mills [20]	1921	125	49·2	36·8
Handley [21]	1922	—	47·0	—
Peck and White [22]	1922	118	—	39·1
Primrose [23]	1923	49	—	44·4
Leeds Series [26]	1926	357	48·7	35·7
Guy's Hospital Series	1926	338	54·1	28·4

The Histology of the Growth in Relation to Prognosis

From a survey of the microscopic reports of the cases examined there appears to be little or no connection between the histology of the growth and the subsequent length of life after operation. The patient with the most atrophic scirrhus may survive only a few months in spite of the most hopeful prognosis, while one with the most cellular growth, unless pregnant, may survive many years.

The Invasion of the Axillary Glands

This invasion of the axillary glands was found to be a factor of much greater prognostic value. A microscopical examination was carried out in 120 of the total 338 verified cases. In 85 cases the glands were found to be invaded by the growth and in 35 cases they were found to be free. The survival period of each group is shown below.

Glands invaded.	85 cases.	
Alive 3 years after operation . . .	39 . . .	45·8%
„ 5 „ „ „ . . .	16 . . .	18·8%
Glands uninvaded.	35 cases.	
Alive 3 years after operation . . .	32 . . .	86%
„ 5 „ „ „ . . .	17* . . .	46%

In Table III the percentage of survivors in each group is compared with the percentage of survivors in the complete series of 338 verified cases.

TABLE III.

To Show the Prognosis with and without Glandular Invasion.

	Total verified cases (338).	Axillary glands invaded (85).	Axillary glands free (35).
Alive at 3 years . . .	54·1%	45·8%	86·5%
Alive at 5 years . . .	28·4%	18·8 %	46·0%

The effect of axillary extension upon the prognosis after operation is very striking. A comparison of the groups is suggestive that in a very large proportion of all the cases traced the axillary glands were invaded by growth. It is interesting to notice that in many cases the tumour was moderately large in size although the axillary glands were found to be free from growth on microscopic examination. It would therefore appear that within limits the size of the growth is of less prognostic value than the condition of the axillary glands. The effect of axillary extension upon the prognosis is borne out by the figures given by the authors of the following series, and is

TABLE IV.

To show Comparative Prognosis with and without Glandular Invasion.

Authors.	Number of cases.	Gland invaded. Alive at		Glands free. Alive at	
		3 years.	5 years.	3 years.	5 years.
Dahl (1925) [24] . . .	83	20·34%	15·79%	70·83%	66·67%
Sistrunk (1921) [25] . .	218	—	18·9%	—	63·0%
Guy's Hospital Series . .	120	45·8%	18·8%	86·5%	46·0%

* Of these 17 cases, 14 are alive and well at the time of writing, and it is probable that the prognosis in this group is even better than it appears.

particularly marked in the Leeds series,[26] where 90·1 per cent. of the cases without axillary involvement were alive ten years after operation.

The Value of Immediate Post-operative Radiation

To determine the effect of post-operative radiation the 338 verified cases used above to determine the general operative prognosis were reviewed, and from these were withdrawn those subjected to immediate post-operative radiation. These numbered 100, and they are compared below in Table V with the remaining 238 cases which were not subjected to this treatment. It should be mentioned that some of the latter received radiation at a later date for recurrence of the disease, but this factor does not affect the general result of immediate or prophylactic radiation. No cases subjected to deep therapy are included.

TABLE V.

To show the Survival Period in the Radiated and Non-radiated Cases Respectively.

Cases subjected to immediate or prophylactic radiation.

Total	100 cases	
Alive 3 years after operation	66	66%
„ 5 „ „ „ „	31	31%

Cases not subjected to immediate or prophylactic radiation.

Total	238 cases.	
Alive 3 years after operation	117	50%
„ 5 „ „ „	65	27·3%

It is evident that the prognosis was very definitely improved in the group subjected to prophylactic radiation, which was carried out on the following lines. The chest wall and the axilla of the affected side from the level of the clavicle to the level of the xiphisternum were divided into four areas, and each together with a fifth area comprising the supraclavicular region was subjected to radiation three times a week during an average period of six months. In some instances this period was considerably exceeded. The voltage used was about 75 kv. and the target-skin distance 20 cms. Each of the above-mentioned areas was given a half-pastille dose (Sabouraud) on each visit filtered through a sheet of " 5 oz. lead " placed close to the skin.

A similar improvement following superficial radiation has been recorded by other writers, as shown in Table VI below.

TABLE VI.

To Show the Effect of Prophylactic Superficial Radiation.

Author.	Cases radiated.		Cases not radiated.	
	Three-year survival.	Five-year survival.	Three-year survival.	Five-year survival.
Lehmann [28] . . .	55%	39%	32·0%	28·0%
Anschutz and Hellmann [29] .	60%	55·5%	48·8%	36·4%
Guy's Hospital Series . .	66%	31·0%	50%	27·3%

Recurrence and Metastasis after Operation

Of the 338 verified cases subjected to operation, it was found that in 195 there was a recurrence of the disease, and in nearly all the cases the date of appearance was ascertained.

The distribution of these recurrences was as follows:

Total cases . 195

(1) Local in skin or scar 103
(2) Glands, axillary and supraclavicular . 86
(3) Bones 23
(4) Other sites 62

In many cases the recurrences were multiple. Each has been included above in the appropriate group.

Local recurrence.—That more than half the total number of recurrences should occur in the scar and surrounding skin is surprising, and points to an inadequate removal of the superficial tissues at the time of operation. In 103 cases of skin recurrence the type of operation performed was as follows:

103 cases:

(1) Local or partial . . 7
(2) Incomplete . . 29
(3) Complete . . . 65
(4) Unknown . . . 2

As regards the amount of skin removed by operation in the respective groups, there is little difference between the complete and the incomplete methods, which together account for 94 cases. A recurrence in the skin after a local or partial removal of the breast is not unexpected.

Regarding the quantity of skin to be removed at the time of

operation, the teaching of Handley is usually followed in this country, and only a comparatively small area of the superficial tissue is removed with the tumour in both the complete and incomplete operations.

Halstead, however, recognised that recurrences were as common in the skin as in the deeper structures, and accordingly practised a very extensive removal of the superficial tissues in the operative field. Since such an extensive removal of the skin precluded the possibility of the flaps meeting after the removal of the breast, the wounds were routinely skin grafted, and Halstead [27] reported the significant observation that he had never seen a recurrence of the disease invade the grafted area.

In the cases under consideration, the average period which elapsed between the operation and the appearance of the recurrence was 28 months. In many cases the recurrence was removed, and it appears that this procedure is almost always worthy of consideration. Many of the patients survived for a varying period of years after such removal, and of all recurrences those which occur in the skin and the scar are the most hopeful as regards both treatment and prognosis. Such recurrences can only be regarded as evidence of inadequate eradication of the disease at the time of operation, and it is probable that their incidence would be less frequent were a more extensive removal of the skin routinely practised.

Glandular recurrence.—In 86 cases of the 195, the recurrence appeared in the lymphatic glands and was distributed as follows:

Axillary glands . . .	31
Supraclavicular glands . .	30
Both groups	25

As in the case of the skin recurrences, those in the glands are relatively early in appearance. The average period which intervened between the operation and the appearance of the recurrence was in the case of the axillary glands 29 months, and in the case of the supraclavicular glands 33 months. A recurrence in the supraclavicular group alone is unavoidable, and indicates that the disease was too extensive at the time of operation to permit complete eradication. In the case of the axillary glands, however, a recurrence after the radical operation can only connote a failure in the complete removal of the axillary lymphatics, although in some cases perhaps this step was impossible owing to the advanced state of the growth.

It is justifiable to assume that the axillary glands are invaded before the supraclavicular glands, and that in the 25 cases where

both groups were affected, had all the axillary glands been completely removed at operation, the supraclavicular extension might not have occurred.

Of the 86 cases of glandular recurrence the axillary glands were affected in 56 cases (*i.e.* 31 axillary glands alone and 25 both groups), and thus account for more than a quarter of the total number of known recurrences.

The nature of the operation performed in these 56 cases of axillary recurrence was as follows:

(1) Local or partial . .	3
(2) Incomplete . .	19
(3) Complete . . .	34

In cases of partial or local removal of the breast a recurrence in the axillary glands is to be expected and is, in fact, only an untreated extension of the disease. The same is true of the cases treated by the incomplete operation. With regard to those subjected to the complete and radical operation, a recurrence in the axillary glands can only mean that the dissection of the axilla was inadequate.

Recurrences in bone. In 23 cases a metastasis occurred in the bony skeleton, and in 6 cases more than one bone was affected. The distribution of the metastases was as follows:

Ribs	7
Femur	7
Sternum . . .	6
Spine	6
Skull	2
Humerus . . .	1
Acetabulum . . .	1

Most of the remaining recurrences and metastases occurred in the liver, lungs and mediastinum. In 22 cases the disease appeared in the opposite breast, and there is no evidence to show whether it was primary or secondary in origin.

In conclusion, with regard to recurrence of the disease after operation, a consideration of the cases under discussion shows that in rather more than one-half the disease reappears in the skin and scar at the site of operation, and in rather more than one-quarter in the axillary glands. Both should be avoidable if the case is operable, the one by the removal of a larger area of skin, and the other by a complete clearance of the axillary lymphatics. Should the case be inoperable and the possibility of completely eradicating the disease be slight, the length of the patient's life is as a rule only shortened by an extensive and

ineffectual operation which is commonly followed by rapid and widespread dissemination of the disease. A survey of the recurrences which take place in advanced cases subjected to palliative removal of the breast leaves much doubt as to the value of this procedure.

Summary

(1) In late cases the less extensive the operation the longer the life of the patient.

(2) In late cases extensive operative interference leads to rapid dissemination and metastasis, and frequently does not confer a greater length of life than is to be expected when operation is withheld.

(3) The operative mortality in all cases was 3·3 per cent.

(4) Of all verified cases treated by operation, 54·1 per cent. were alive at 3 years, and 28·4 per cent. were alive at 5 years.

(5) When the axillary glands are not invaded by growth at the time of operation, the prognosis is very materially improved: 86 per cent. of such cases were alive at 3 years, and 46 per cent. at 5 years.

(6) When the axillary glands are invaded by growth the prognosis is less favourable: 45·8 per cent. of such cases were alive at 3 years, and 18·8 per cent. at 5 years. It is probable that the majority of the total number of cases in the series belonged to this category.

(7) Superficial radiation applied immediately after the operation has definitely improved the prognosis of the disease.

(8) More than half the recurrences after operation were found in the scar and adjacent skin, and more than a quarter in the axillary glands. Both were relatively early in their appearance.

The thanks of the writers are due to the Surgical staff, to Dr. C. E. Iredell and to Dr. G. W. Nicholson for their kind permission to consult the records of their respective departments, and also to Col. A. B. Smallman and Dr. Lane-Claypon of the Ministry of Health for their kind advice.

APPENDIX

Total number of cases . . .	722
Side affected:	
Right side	326
Left side	325
Unknown	71

Age Incidence

Age groups.	Number of cases.	Single.	Married.
15–19	2	2	0
20–24	1	0	1
25–29	7	1	4
30–34	32	8	21
35–39	72	10	53
40–44	122	19	75
45–49	132	11	100
50–54	115	19	74
55–59	88	9	62
60–64	63	5	48
65–69	48	4	34
70–74	17	4	9
75–79	9	1	6
80–84	1	0	1
85–89	1	0	1
	710	93	489
Age unknown .	12	Civil state unknown	140
Total .	722		

Situation of the Tumour in the Breast

	Right side.	Left side.
Upper and outer quadrant . . .	110	68
Upper and inner quadrant . . .	18	25
Lower and inner quadrant . . .	11	6
Lower and outer quadrant . . .	20	27
Central	28	37
Upper	12	18
Lower	6	6
Inner	3	5
Outer	5	2
Axillary tail	0	1
	213	195
Situation unknown	113	130
Total	326	325

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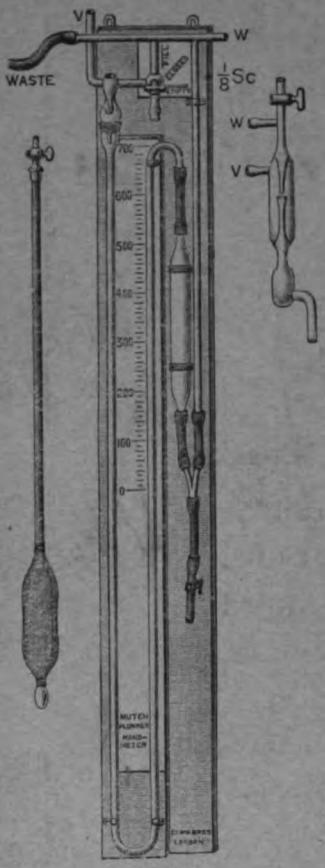

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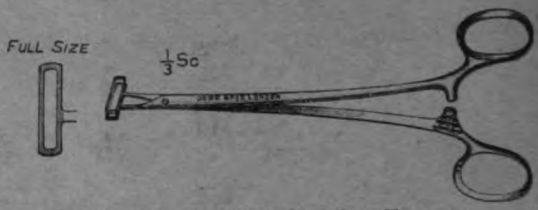

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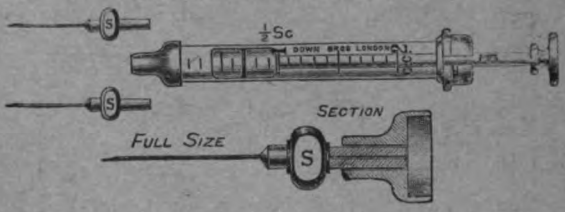

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