III.—*Experiments with Smeared Virus.*

In this experiment the material used was a mixture of the blood and throat secretions of a scarlet fever patient. This patient, a young man of 22, had had measles and had been vaccinated; his general health had always been good. The present illness began on March 6th, 1921, with sudden shivers and fever; scarlet fever was diagnosed by a physician, and on the 8th patient entered the Kitasato Institute Hospital. On the 10th, when I collected the material, he had eruption all over the body, the tongue was coated pale white, the tip was a bright scarlet colour; temperature 37.4°C . The throat secretion was obtained after careful gargling, and the blood was taken from the median vein as in the previous cases. To determine the presence of the virus in the materials collected, the secretion was subcutaneously injected into monkey No. 148 and the blood into monkey No. 146. The former had fever of 40°C . on the 15th day, lasting for five days; the latter had fever on the 7th day, rising on the 10th day to 39°C . with eruption over the face, especially around the eyes. These symptoms agreed with those of experimental scarlet fever in man.

Throat secretion and blood were mixed and a cotton pledget, soaked in the mixture, was carefully smeared over the mucous membrane of the tonsils and throats of the children who had received prophylactic inoculation. As virus smeared over the mucous membrane was liable to carry infection to others, the two oldest children, who were attending school, and the youngest, who was still at the breast, were excluded from this experiment; only the boy I. and the girl H. received the smeared material. For the next three weeks I carefully examined the temperatures, urine, and throats of the children, but there was nothing to be noted at all. Thus the inoculation completely protected the children from the disease.

IV.—*Summary.*

From the foregoing experiments it is clear that prophylactic inoculation against scarlet fever with the blood of a patient, taken before the eruption appears and given subcutaneously in an amount of 0.0001 c.cm., causes not only no local or general symptoms in man, but protects him from infection. Even an injection given 50 days after inoculation with the blood, and smearing the children's throats with the mixture described above, 115 days after inoculation, did not give rise to the disease.

It has been claimed by some investigators that one-third of human beings have a natural immunity against scarlet fever, and perhaps my children had this natural immunity. Moreover, it has not yet been determined that the dose of blood given in the infection experiments was enough to infect the children. Taking these facts into consideration, I cannot claim that these experiments are flawless; but considering the results which Dr. Kusama obtained with typhus fever, the fact that the experimental objects were of the most susceptible age, and the fact that the control monkeys showed the presence of the virus in the material used for the smearing, it is not an overstatement to say that the experiment strongly suggested the efficiency of prophylactic inoculation against scarlet fever.

On the effective period of immunity and its time of appearance after inoculation will be reported later.

My thanks are due to Dr. Kusama, who has given me valuable guidance, and to Dr. Karube, Dr. Sukekawa, and Dr. Miyajima, who have greatly assisted me.

LITERARY INTELLIGENCE.—The twelfth edition of Bruce and Dilling's "Materia Medica and Therapeutics" is announced for immediate publication by Messrs. Cassell.—Messrs. J. and A. Churchill have just issued a 48-page catalogue of medical and scientific publications. The forthcoming appearance is announced of "An Introduction to Biophysics" by Dr. D. Burns, Grieve Lecturer in Physiological Chemistry at the University of Glasgow, with an introduction by Prof. D. Noel Paton, F.R.S. The subjects dealt with include energetics, cellular mechanics, cell communities, transport, and the organism as a whole.

X RAY TREATMENT OF TWO CASES OF OTOSCLEROSIS.

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IN dealing with otosclerosis we are "confronted with one of the most difficult and obscure problems in modern medicine" (Gray). And because its aetiology and essential nature are still largely unknown or in dispute, and its course one prolonged usually over so many years (often with intermissions or natural arrest), to make an estimate of the true value or otherwise of any treatment is a matter of the greatest difficulty. In well-established cases, which are perhaps the great majority of those presenting themselves, permanent bony damage has already taken place at the stapes-foot, with possibly secondary nerve impairment, and such cases afford no fair test of the value of radiation treatment, any more than late inoperable malignancies, old-standing exophthalmic goitres or (as I have noted) acromegalties. It is only in the earliest stages when there are young actively proliferating or hyper-functioning cells that radiation can be expected to benefit to a satisfactory degree. Now, unfortunately, as Brühl says, otosclerotic patients rarely notice the earlier tinnitus or slight impairment of hearing, and therefore do not usually apply for advice till the newly-built bone at the annular ligament of the oval window has reduced the hearing to a marked degree (whispering reduced to 0.5 m. or less). This being so, there is nothing to be wondered at that some otologists hold the view, and frankly tell their patients, that it is an "incurable" complaint.

Prof. Siebenmann, the eminent oto-laryngologist at Bâle, has been experimenting since 1912 with radiation treatment, encouraged, at the beginning, with the good results obtained by radiation of an otitis fibrosa case (as he remarked at the Oto-laryngological Congress at Kiel in May, 1914), and while awaiting an analytical report from him on the results of his many hundred cases, it may be of interest to bring the matter forward, discuss the rational basis for the treatment, and give the results of two cases treated.

Theories as to the Cause and Nature of the Disease.

There are about ten distinct theories as to the cause and nature of the disease. The earliest opinion was that it is secondary to middle-ear inflammation (of mucous membrane or periosteum); later views are that it is a primary condition, either a bone disease or an abnormal development of the cartilaginous remnants in the labyrinth capsule, or is due to vascular conditions (active hyperæmia, anaemia, and venous congestion each having supporters). Then there are toxic and bacteriological, internal secretion, and chemical theories; and there is the nervous theory, that the sometimes associated degeneration of the labyrinth nerve is primary, and the bone change secondary to this; and the developmental theory, that there is arrested development or degeneration of the organ of hearing as a whole, central and peripheral. There seems no doubt that many factors can excite its appearance in a predisposed person. Brühl, in this connexion, gives authorities for syphilis, arteriosclerosis, chills, internal secretion changes, latent tetany, rheumatism and gout, uræmic intoxication, scrofula, anaemia, rickets, osteomalacia, auto-intoxications, tuberculosis, tropho-neurosis, and wasting diseases. The hereditary nature is most marked, as with bony abnormalities (polydactylism, multiple exostoses, &c.) and some bone diseases (Paget's disease, achondroplasia).

Katz was the first (1890) to publish the microscopic findings in a case diagnosed during life as a stapes-ankylosis. Toynbee (1863) and Tröltzsch (1881) had called the condition "sclerosis," and for long it was

considered a special form of chronic middle-ear "dry catarrh." Moos, in 1867, and Politzer, in 1893 and 1901, gave reasons for considering it a primary disease of the bony labyrinth, as in the great majority of cases the middle-ear mucous membrane was found perfectly normal, while in many preparations the most marked changes were found in the deeper layers away from the mucous membrane. Specimens were soon noted which showed scattered islets of similar bony changes throughout the petrous bone, with or without stapes involvement. Further, labyrinth-atrophy was sometimes met with on the affected or on the opposite side, and Manasse brought forward a nerve-degeneration theory which was supported by many. Brühl, in an excellent recent summary of our knowledge of the disease, points out that the facts suggest rather that labyrinth-atrophy, when met with, must be secondary (or a post-mortem change), Manasse himself having demonstrated a preparation showing stapes-fixation without definite labyrinth change, and in his more recent works (1914 and 1917) coming nearer to Brühl's view that the primary change is in the bone. As to vascular theories, O. Mayer, Cornet, and Gray have all wholly or largely given up earlier theories of theirs as to its origin in local anæmia (arterio-sclerosis, syphilitic endarteritis, or thrombosis), and this clears the ground somewhat for a basis for radiation treatment. Mayer now considers it an "undescribed variety of otitis fibrosa," an "osteofibromatosis." Instead of anæmia there is increased vascularity (clinically suggested by the sometimes seen "flamingo-red" flush on the promontory), it presents appearances like Volkmann's "vascular otitis," is a "chronic metaplastic otitis" (Manasse), and has apparently close relations with osteomalacia. As Ferreri says, there seems "a great affinity" between osteomalacia, rickets, and otosclerosis. All the patients in Arcangeli's clinic with osteomalacia also had otosclerosis, and on this relationship Siebenmann's phosphorus treatment is based, whether increased ovarian internal secretion (with hyperæmic results elsewhere) or that of other endocrine glands, or calcium (Kobrak) or chloride (Cornet) retention be ultimately at fault. It must frequently at least be an endocrine gland anomaly, as Alexander has found otosclerosis in cretins (human and animal). Gray regards it now biologically as a "variation," a degeneration of the later-evolved auditory as distinct from the equilibrative mechanism of the ear (the latter fully-developed already in fishes, the former appearing with reptiles or early amphibians).

Siebenmann, on the other hand, regards it, on the basis of many histological researches from his clinic, as an over-development in the labyrinth of cartilage remnants which normally are there at least till adult life (Taniyama), especially in the region in front of and above the oval window. The labyrinth is practically full-size at birth, and if it continues to develop in the confined space it is in (Kerrison), as the skeletal bones normally do, by absorption and new bone formation, there must be marked changes, beginning, in Siebenmann's view, at the boundary of the original cartilaginous and the later periosteally developed labyrinth-capsule. (Brühl thinks the predilection for the region in front of the oval window is due to the bony stresses set up by the pull of the tensor tympani muscle. Gray thinks that in addition the stresses set up by the continual stapes-vibrations sensitise the bone in the neighbourhood to new formations or pathological changes.)

The earliest changes are rather matter for dispute, Brühl finding them in the vessel-canals of the old periosteal bone, absorption of the bone round these, and subsequent new building of an abnormal spongy bone; Mayer, in the transformation of the connective-tissue cells of the marrow and vessel-canals into osteoblasts and osteoclasts, so that "this richly cellular fibrous marrow causes on the one side an absorption, and on the other a new growth of bone" (1912). In both otitis and otosclerosis are found, as Sohler Bryant, in his exhaustive analysis of the

ætiology of the condition (1913) points out, increased vascularisation, granulation tissue, replacement of the normal bone by osteoid tissue, exostosis and hyperostosis, a definite line of demarcation (Pommer's cementing line), the formation of giant-cells, origin in the endosteum or periosteum, cellular marrow transformed to fibrous, and finally new atypical compact bone. Bryant calls it an "osteodystrophy." The marrow is atypical, as myelocytes and normoblasts are absent (Wolff). The giant-cells are of interest; up to 12 nuclei have been seen (Jenkins).

As Denker in his analysis of the 26 or so cases, and literature to 1904, gives nearly five pages of references, and Bryant, in 1913 (writing on the ætiology chiefly), gives seven and a half pages of references in small print, it is clear the subject is an immense one. The main point for the present purpose is that the pathology of the condition suggests that in its early stages it should be amenable to radiation treatment. Diathermy has been found to give bad results (Joseph); more is to be hoped for from the "ischæmic power of radiotherapy" (Chevriat and Bonnot), and its action on certain types and growth-stages of cells. Additional grounds for believing the treatment may be of avail are (2) the effects of radiation on growing cartilage and bone in young animals (Récamier); (3) the well-known curative effect of radiation on tuberculous bones and joints (Albert-Weil, Wetterer, Iselin, Petersen, &c.); and (4) the results of radiation on young osteomata (Chevriat and Bonnot).

Early Results of Treatment.

The first to try X ray treatment in otosclerosis, so far as I am aware, was Jaulin, in 1908. He applied 1-2 H weekly (5-7 Benoist) through an ear-speculum, the rays directed on the tympanum. 3-14 sittings were given. Of ten cases six improved: he stated they improved more in their voice-perception than could be shown by objective tests; tinnitus also improved. Schwartz treated three cases with six doses at monthly intervals, in one case with surprisingly good results, the hearing becoming practically normal; one showed no improvement, the third was slightly better. Ortloff, in Freiburg, reported ten cases in 1913, with negative results as regards improvement, a "middle-soft" Müller water-cooled tube being used, a third of a pastille being given on each of three successive days, then a 2-3 weeks interval, then another series (sometimes a pastille dose being given at one sitting with 2-3 weeks pause). Two or three series were usually given, in one case four series. The dose was measured apparently (being an unfiltered pastille dose) to the external ear: Jaulin calculated his one or two-fifth dose to the tympanum. Ortloff was not very fortunate in his choice of cases, only one had a history of one or two years (Case 6), some having eight or ten years' history of deafness. The results on the hearing, tested by Prof. Bloch's elaborate scheme, were uniformly negative; if there was slight improvement it was invariably followed by return of the tinnitus and deafness as before. (The possibility of therapeutic aim at *arrest* of the process is briefly referred to in conclusion.) As the tube-size and distance are not given it is impossible to compare the doses given by Jaulin and Ortloff, but considering the position of the oval window (behind the post. inf. quadrant of the tympanum, but partly hidden in 32 per cent., and quite hidden from the tympanum in 19 per cent.—refer. in Ortloff), and the necessity for penetrating the bone, even in the case of the most favourably placed oval window, to at least 3-4 mm. with sufficient radiation, neither Jaulin nor Ortloff seems to have used a sufficiently penetrating ray, or enough total dosage. The difficulties are certainly great. Siebenmann's cases have been treated on another scheme, and, while I should not be justified in publishing the complete technique used at Bâle (being the as yet unpublished work of others), it may be said that a cross-fire method is used on to the fenestra ovalis, with a 4 mm. filter. Schemes of fractional and full

doses have been worked out, and the total dose advisable for each ear has been the subject of investigation. A certain amount of hair-fall takes place, temporary only, but no deleterious effects have been noticed on the labyrinth, dura, brain, hypophysis, or in other ways. Coolidge or Müller's boiling tubes are used. (I should be glad to give fuller details of the technique to any interested who write to me.) During a visit to Bâle Prof. Siebenmann kindly gave me fully his views as to the theoretical grounds for the treatment, and explained that he advises it in late cases with the hope of arresting the process at the stage it is in, and in early cases with the hope, and in fortunate cases with the result, not only of arresting it, but of causing some slight improvement. No more, considering the pathology of the condition, can be hoped for. It might be of use in certain cases to combine ovarian radiation with the ear radiation (see Wetterer on beneficial results with ovarian irradiation in osteomalacia). In a recent communication (June 16th, 1921), Siebenmann writes that "his trial of the method has not continued long enough for him to come to a definite conclusion on the matter"; he began "with a good dose of optimism," but the results "are only to a small degree positively encouraging." As a number of radiation schemes have been used, and these only in the last four years to any considerable extent, it is still too early to hope for much in the way of results. But the method seems to deserve full investigation, as even if the treatment only arrests the usually inevitable progress of this common and disabling complaint (perhaps even only in certain types of cases, as may be defined by further research on the subject), it will have achieved a great therapeutic success in a region which hitherto has been, for the most part, a despair of the internist and the otologist, and, as a result, a "happy hunting ground" for the quack in various forms and disguises.

The Author's Cases.

My two cases are as follows:—

CASE 1.—Mr. F., aged 37, no hereditary history, R. ear began to be affected 15 years ago, L. ear about 10 years ago, had consulted many of the leading otologists in England, and tried pneumo-massage, &c., had been told it was almost certain to progress slowly and was incurable. On a visit to Switzerland, in the spring of 1920, with the hope that the high dry air for some months might effect some improvement, he consulted Prof. Siebenmann, who recommended X ray treatment as the only thing likely to arrest the course of the disease. Recommended to me by a medical friend of his. Being very sceptical as to possible benefit, I made a visit to Bâle, after some correspondence with Prof. Siebenmann, largely also to choose between the various schemes of radiation employed. The patient understood that the most that could be hoped for was arrest, which he greatly desired, as his wife said he was worse than he was six or eight months ago, and any further increase in his deafness would cut him off completely from social enjoyments. Tympani were normal, no operations had been performed (though one had been recommended in the nose), whispering heard at the ear only, R. ear with C fork, Rinné -12, L. ear -7. After the treatment, as anticipated, there has not been any change whatever to remark on; the watch was heard, if anything, slightly further away on the left side than before (from 1-1½ in.). So far the condition seems stationary, both as regards hearing and tinnitus. It will require another year or two to show if it is progressive.

CASE 2.—Miss H., aged 25, no hereditary history was made out, but a brother and a sister show signs of the disease coming on. No operations, but a history of nasal catarrh. She was referred to me by Dr. J. W. Stenhouse, and as she was attending the Ear Hospital, under Dr. Frank Wrigley, he kindly saw her before I began treatment, and wrote that as "he was quite sure she was not going to improve with the ordinary methods of treatment, it would be quite worth while to try X rays." He viewed her as a mixed otosclerosis and catarrhal case. R. ear began about eight years ago, left not until about seven months ago, since when it had become rapidly worse, and she was in danger of losing her employment (office work). Marked tinnitus both low and high. Paracusis Willisii. Watch at R. ear at ¼ in., L. ear about 1 in. R. ear, Rinné -6; L. ear, Rinné -6. After treatment over three months she had distinctly improved, could hear a clock at her home that she had not heard for eight months, the low-toned tinnitus in the left ear was much less, and was away for considerable

periods (Ortloff's fifth case showed improvement in the low tinnitus—? vascular, of hyperæmic origin, Mayer, Brühl, &c.), and Dr. Wrigley, examining her on April 30th, found definite improvement on both sides; she could hear his watch (a softly-ticking one), which she had not previously been able to do. Treatment was continued, and the improvement maintained. On June 16th the watch was heard at R. ½ in., the L. 1½ in. In letter of August 15th the improvement was reported as continuing, "can still hear the clock." It is hoped that this slight but definite improvement will be maintained, and in any case that the process has been arrested, as Siebenmann finds is sometimes apparently the case.

My thanks are due to Sir William Milligan and Dr. Frank Wrigley for their interest and encouragement, and to Prof. Siebenmann for his kindness and patience in correspondence and on my visit to his clinic, and to Dr. Löffler and the sister-in-charge of the Röntgen work, at the Physical Treatment Department of the Bürger-Spital, Bâle, for their kindness in giving me details as to the method of treatment.

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