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GUY'S HOSPITAL REPORTS

EDITOR:

ARTHUR F. HURST, M.D.

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CONTENTS

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CHRONIC URTICARIA AND ANGEIO-NEUROTIC ŒDEMA DUE TO BACTERIAL SENSITISATION

By H. W. BARBER, M.D., Physician in Charge of the Skin Department, Guy's Hospital.

In a previous communication [1] cases of chronic urticaria were described, in which the eruption was proved to be due to focal sepsis, and, as the association does not appear to be generally recognised, the publication in detail of some other cases of this kind is desirable. Judging from my own experience, I am now inclined to think that in the majority of patients, in whom chronic or recurrent urticaria, with or without angeio-neurotic symptoms, appears for the first time in adult life, the underlying cause is sensitisation to bacterial rather than to food proteins. The same is true, I believe, of asthma and of that type of eczematous dermatitis which is apt to be associated with asthma. Food sensitisation has, I am convinced, been greatly exaggerated as a causal factor in asthma among adults, and I am unable to explain the number of positive cutaneous reactions towards food proteins obtained in these cases by the American school. While admitting the importance of sensitisation to animals—horse, cat, dog, and birds,—I am in entire agreement with Dr. A. F. Hurst that it is exceptional in this country to obtain positive cutaneous reactions to foods in adult cases of asthma, although that type of child, who from his earliest days suffers from asthma, bronchitis, and a certain variety of eczema, usually gives very definite reactions to a number of foreign proteins. As the child grows older, however, I believe that it is bacterial sensitisation that comes to be the important factor, for immunity to food substances is as a rule gradually acquired. Most American writers lay no stress on bacterial sensitisation as a cause of chronic urticaria, and in a recent French text-book of dermatology it is not even mentioned, despite the fact that a great deal of work is being done in France on the relationship of urticaria to the phenomenon of anaphylaxis. On the other hand, Haldin Davis [2] states that " hidden sepsis is the most likely cause " of chronic urticaria.

The question of course arises, why, since some degree of focal infection is so common as to be almost universal, pathological symptoms referable to it only occur in certain cases, and why such symptoms differ in different individuals. The problem is bound up with the phenomenon of sensitisation, and although, perhaps, everyone is capable of becoming sensitised to some toxin or other, some individuals and members of certain families are much more liable than others. Asthma, urticaria, angeio-neurotic œdema, and certain forms of eczema may be looked upon as the outward and visible signs of sensitisation, and in their causation an hereditary susceptibility is undoubtedly often an important factor, and also a peculiar instability or hyper-excitability of the nervous system, which is easy to recognise clinically, but which we cannot at present define. In the case of bacterial sensitisation it will often be apparent that the sensitivity has developed during an acute infection, and if, after the subsidence of the acute attack, a local residual focus is left, in which the infecting organism to which sensitisation has occurred remains active, chronic or recurring symptoms of sensitisation, *e. g.* urticaria or asthma, are likely to develop. It is for this reason that foci of infection are of importance, apart incidentally from the fact that direct bacterial invasion of the blood stream may take place from them. In the case of abscessed teeth, of a chronically inflamed appendix, and of suppuration in the nasal sinuses even the most conservative advise removal of the focus of infection, but in the case of the tonsils the decision is not so easy. At the outset it cannot be too strongly emphasised that mere enlargement of the tonsils is no indication for their removal, and conversely that, if they are small, it does not follow that they are not a source of infection. Their enlargement in children, which is part of a general hyperplasia of the lymphoid tissue of the nasopharynx and pharynx, is doubtless due to chronic catarrhal infection, and this in its turn depends on improper feeding and unhealthy surroundings; the hyperplasia is a local defensive mechanism, and removal of the tonsils and adenoid vegetations, though sometimes advisable on mechanical grounds, will not ensure against recurrence of the infection, but, on the contrary, may predispose to it spreading downwards to the lower parts of the respiratory tract. The indiscriminate removal of tonsils and adenoids in early childhood that obtains at the present time is entirely indefensible. In older children and adults the state of affairs is different. Either as a result of severe attacks of tonsillitis, quinsies, or often *owing to a previous incomplete operation on the tonsils,* scarring may have occurred,

the openings of several crypts may have been obliterated by scar tissue, and actual abscesses may be present in the tonsillar substance. In several of my cases, in which the tonsils were a source of virulent infection, one or more operations had already been performed on them, and it cannot be too strongly insisted that anything short of complete enucleation is not only useless, but actually dangerous. In short, the tonsils are a source of infection if they contain septic matter—not merely concretions in the crypts, which are of little or no moment—shut up within their substance; injection of the anterior palatal folds and of the tonsillar tissue, the presence of septic matter, and definite enlargement of, with attacks of painful swelling in, the lymphatic glands draining the tonsils, are the main indications for their complete removal.

Just as asthma may be due to more than one variety of micro-organism, so an urticarial eruption may depend on sensitisation having occurred to a *Streptococcus longus*, the *Bacillus coli*, a *Staphylococcus aureus*, and possibly other bacteria. Probably a *Streptococcus longus* is most commonly responsible. One point of importance is that a previous history of rheumatic fever is not uncommon in these cases; two of the patients in this series had had it, and I have recently seen two others, who came to me for persistent urticaria, both of whom had chronic rheumatic valvular disease.

I have had a few cases in which the teeth were apparently the main source of infection, and in which recovery followed extraction of septic roots and treatment of pyorrhœa, with or without subsequent vaccination with an autogenous streptococcal vaccine. In one case a chronic appendicitis was almost certainly the cause. The patient, a woman, had suffered continuously for about eighteen months from severe urticaria, which the most rigid dieting failed to relieve. Careful examination disclosed no obvious source of infection, except a very tender appendix; its removal two years ago was immediately followed by a most violent attack of the eruption, but since then there has been no recurrence. Oberndorf[3] also has reported a case of angeio-neurotic œdema, which yielded immediately to the removal of an inflamed appendix. By the courtesy of Dr. A. F. Hurst I am permitted to reprint a most interesting case described recently in the *Practitioner*.[4]

Case I. Urticaria following septic wound of thumb; recovery fourteen years later after treatment with vaccine, made from streptococci isolated from a tooth.—Miss M., a nurse, aged 38, had a severely poisoned thumb in 1906, for which she was off

duty for three months. She had never had any skin trouble, and had never suffered from asthma or hay-fever. About three months after her recovery urticaria appeared on the middle of the same forearm. It remained for a few weeks and then disappeared. After this it came and went, the attacks becoming gradually longer and occurring at shorter intervals, both arms being now involved. From October 1919 to April 1921, when she was admitted into New Lodge Clinic under my care, urticaria had been present in both arms without intermission.

She had experimented with almost every variety of food, omitting one after another from her diet for periods of a fortnight and sometimes of three or four months, but without benefit. For eighteen days she had taken nothing but milk, but the rash underwent no modification.

No obvious cause of the urticaria could be found, and the cutaneous reactions to the proteins of numerous foods and animal emanations proved negative.

The history suggested that the urticaria might be due to sensitisation to the organism which had caused her poisoned finger fifteen years ago, and that she had subsequently become infected elsewhere with this organism, at first intermittently and later continuously, and that the urticaria was a result of this sensitisation. She had had twenty-four teeth extracted in 1902 for abscesses round their roots, and her remaining teeth were found to be septic. The worst one was removed, and a streptococcus and *M. catarrhalis* were isolated from the granular tissue at the root.

On May 16 an autogenous vaccine containing five million streptococci was given. This caused a slight increase in the urticaria. Each subsequent injection caused a temporary aggravation of the urticaria, which improved in the intervals between the injections, together with pain in the arm, slight pyrexia, pain and, at first, discharge in the socket from which the tooth was removed, and with the larger doses *pain in the thumb and discharge from the wound*, which had been healed and free from pain for fifteen years.

The urticaria had greatly improved by July 15, four days after the sixth injection; during the next six days only three small spots were present. On August 15 it disappeared completely, but returned for a few days after each of the next ten injections. After the remaining two injections it reappeared only to a very slight extent, and since September 22 there has been no trace of urticaria, except for a very slight return in November, which only lasted for four days.

Comments.—It will be noted that in this patient several teeth were removed for abscessed roots *four years before* the infection of the thumb occurred. The latter infection may have been *via* the blood stream, *i. e.* a streptococcus from a remaining abscessed tooth may have infected the thumb, possibly after

local trauma, or, of course, the infection may have been an external one. In any case the streptococcus in the teeth and in the thumb must have been of the same strain. Sensitisation to the organism presumably occurred during the acute infection of the thumb, and the presence of foci of infection with the same streptococcus in the teeth accounted for the persistent urticaria. The observation that, with autogenous vaccine treatment, pain in the thumb and discharge from the wound occurred fifteen years after it had healed is of enormous importance, illustrating as it does how long micro-organisms may remain latent in scar tissue.

Case II. Chronic urticaria and angeio-neurotic œdema due to suppuration in the left antrum and frontal sinus.—Mrs. H., aged 46, consulted me in May of this year for the most violent urticaria with angeio-neurotic swellings, which appeared first in the previous February. Various changes of diet, purgation, and sundry drugs had been tried without avail. The insomnia produced by the irritation had led to considerable exhaustion. As a child she had been very subject to colds, but of late had only had two or three every winter. Twelve years previously she had had a nasal discharge on the left side with tenderness over the left antrum, and she had since had an occasional bad smell in the nose. In December 1921—two months before the onset of the urticaria—she had a heavy cold, and three weeks before she came to me she had another, which followed an injection of anticatarrhal vaccine, and was accompanied by sore throat and an intense exacerbation of the urticaria. She had recently had neuralgic pain over the left frontal region.

In ordinary routine examination I found muco-pus dripping from the left side of the nasopharynx, and there was some tenderness over the left frontal sinus. I therefore asked Mr. Zamora to see her, and he reported :—

"*Tonsils* normal; *larynx* normal; *left antrum* opaque to transillumination."

Mr. Redding, on x-ray examination, reported :—

"Greatly increased opacity of *left frontal sinus and left maxillary antrum*, indicative of empyema. The left ethmoidal cells show very slight loss of translucency, probably due to slight œdema of the mucosa. Right side normal."

Mr. Zamora operated 18.5.22. Intranasal drainage of the antrum and frontal sinus and scraping of the ethmoid region were performed. The antrum and ethmoidal cells drained well, but after a time there were again signs of retention in the frontal sinus. A second operation was undertaken, 9.7.22, the left frontal sinus being opened from the exterior and found to contain polypoid granulations, which were obstructing drainage to a certain extent. After this second operation the local condition recovered completely.

The urticaria became much less after the first operation,

but returned when further retention occurred in the frontal sinus. It disappeared completely three days after the second operation, and she has not had another attack up to the time of writing.

Cultivations of the pus from the antrum and frontal sinus gave only a few colonies of staphylococci, and no streptococci were found; it is probable, however, that a streptococcus was the original infecting organism.

Comments.—This case illustrates very well the importance of the nasal sinuses as a possible source of latent sepsis. Had I not happened to observe the muco-pus in the nasopharynx I should not have suspected sinus disease, as the patient made no mention of her previous nasal discharge until closely questioned. This is the only case of urticaria due to sinus infection that I have yet encountered, but I have three patients in whom lupus erythematosus was associated with chronic antral and ethmoidal infection.

Case III. A chronic erythemato-urticarial eruption associated with acute rheumatism. Recovery after enucleation of the tonsils. —Mrs. S., aged 35, came to me in April 1921 for a chronic erythemato-urticarial rash, which had appeared for the first time seven months previously and was attributed at the time to sea-bathing. She had suffered from recurrent attacks of tonsillitis as a child, and one preceded the outbreak of the eruption. Two months after its appearance (November 1920) she had an acute attack of rheumatic fever accompanied by sore throat, swelling of the joints, and high fever. At this time the rash was so severe that scarlet fever was suspected, and Dr. Goodall was called in consultation. He diagnosed acute rheumatism and considered the eruption to be a rheumatic erythema. After remaining in bed for six weeks she recovered from the rheumatism, but the rash persisted. It appeared chiefly in the evening and after exertion or excitement, was intensely irritable, and, as its sites of predilection were the neck and shoulders, she was prevented from wearing evening dress. There is little doubt that the patient also had evening pyrexia at times, although she did not take her temperature. The pulse-rate even at rest was increased, and there was evident vaso-motor instability as shown by alternate flushing and pallor of the skin. Various dietary experiments had been tried before I saw her, but without effect.

The history of repeated sore throats in childhood, the fact that the outbreak of the eruption was preceded by sore throat, as was also the attack of rheumatism, and that during the latter the rash was very intense, suggested to me the probability that sensitisation to a streptococcus had occurred, the eruption being a manifestation of this. Everything pointed to the throat being the source of infection, although at first sight it was not

obviously septic. *The teeth* appeared in good order, but no radiograms were taken. Careful examination showed that the tonsils were scarred and definitely septic, and a *right tonsillar gland* was much enlarged and slightly tender. There was no evidence of appendicular or gall-bladder infection, and the lungs and heart were normal. Cutaneous tests to *stock* proteins of *Streptococcus viridans*, *S. non-hæmolyticus*, and *S. hæmolyticus* were negative.

At my request Mr. Zamora examined the patient and reported that there were no signs of sinus disease, but that the tonsils were clearly a possible source of infection. The rational line of treatment seemed to be enucleation of the tonsils, followed, if necessary, by the giving of autogenous streptococcal vaccine prepared from them with a view to " desensitising " the patient.

Enucleation of the tonsils was performed on May 1, 1921; the operation was followed by a profuse outbreak of the rash and considerable pyrexia. The temperature remained raised for about ten days, an unusual thing after this operation. The patient went away to the sea, and returned much improved in general health. She no longer felt as though she had fever in the evening, and the vaso-motor instability was not so marked. The rash, though very much less, still appeared slightly from time to time, and it was decided to give a course of autogenous vaccination with organisms cultured from the tonsils. These were a streptococcus longus, which greatly predominated, and a micrococcus paratetragenus. *An intradermic test with the vaccine prepared was definitely positive;* a control, using stock staphylococcal vaccine, was negative.

About twelve injections were given in increasing doses. They appeared to have two definite effects—one to provoke a slight outbreak of the urticaria, the other to cause *the enlarged right tonsillar gland to swell up and become tender.* This focal reaction in the gland occurred after several, but not all the injections, and became progressively less. The patient has now been free of the eruption for over a year, and her general health is excellent.

Comments.—In this case there was a history of repeated sore throats, and sensitisation to the infecting organism—a streptococcus longus—presumably took place during the attack which preceded the initial outbreak of urticaria. Enucleation of the tonsils was considered advisable because (1) they were scarred and septic, (2) a right tonsillar gland was enlarged and tender, (3) the patient had had an attack of acute articular rheumatism, and (4) there had evidently been continuous evening pyrexia suggesting constant infection from this the only source apparent. The slight persistence of the urticaria after operation was doubtless due to the existence of a secondary focus in the enlarged right tonsillar gland; the focal reaction

in this gland alone makes this almost certain. It is the presence of such secondary foci in lymphatic glands and probably in the intestines that doubtless accounts for the persistence of symptoms of infection when main and primary foci, such as teeth and tonsils, have been removed. It is important to note that cutaneous tests with stock streptococcal proteins were negative, whereas an intradermic test with the patient's own vaccine was positive. Owing to the specificity of different strains of bacteria, cutaneous tests with stock bacterial proteins are seldom in my experience of any value.

Case IV.—This case was strikingly similar to the last, but the urticarial eruption was, when at its worst, accompanied by angeio-neurotic swellings.

Mrs. A., aged 30, was brought to me in consultation in January of this year on account of recurrent urticaria, which began in the form of occasional attacks at the age of twenty. She had had rheumatic fever at the age of thirteen, and was in bed with swelling of the joints for some six weeks. Her teeth were all removed in 1914, and in the same year her tonsils were operated upon on account of repeated sore throats. Early in 1918, when in America, her attacks of urticaria became very severe, and on returning to England she was operated upon by a well-known gynæcologist for pyosalpinx, and was told that it was unlikely she would ever bear children. She remained comparatively free from urticaria for some months after this operation, but later the attacks returned. She was then treated by a bacteriologist with injections of vaccine prepared from the fæces (? *B. coli* vaccine), and of iron and arsenic. This treatment brought about improvement in her general health, and her urticaria was less severe. At Christmas 1921, however, she had a most severe attack with high pyrexia and intense swelling of her face, so that she was unrecognisable; it began "as though she had influenza" with shivering and pains all over, and she had noticed similar symptoms with previous severe attacks. Needless to say attempts had been made to incriminate various articles of food, but it was found that dieting made little or no difference, and she was never able to associate the severe attacks with any particular food substance.

The patient was a fair-haired, healthy-looking woman with the same tendency to sudden flushing and pallor as was remarked in the case just described. *The teeth* were all false. *The tonsils:* Although tonsillectomy had been performed seven years previously, only the upper poles had been removed, and the lower poles were large and lobulated, extending far down the pharynx; the tonsillar glands were enlarged. The patient had noted that these glands sometimes swelled and became slightly painful. Examination of the chest and abdomen revealed nothing abnormal.

The fact that the severe attacks of urticaria were accompanied by febrile symptoms and definite pyrexia, and that they appeared to bear no relationship to diet, seemed to point to some latent infection being the cause. The history of rheumatic fever in childhood and of repeated sore throats, and the fact that the tonsil operation had left scarred remains, made me suspect a throat infection as the original cause of bacterial sensitisation having occurred, and the tonsillar remains as a possible source of infection. On the other hand, we had to consider the apparent improvement that had followed the operation for pyosalpinx and also the injections of fæcal vaccine. For this reason it was considered advisable to have a complete pelvic examination made, and to investigate the fæcal flora. The former revealed no evidence of latent pelvic infection, and no abnormal organisms were found in the fæces. The urine was also normal. Moreover, Mr. Skene Keith found the complement-fixation test to the gonococcus completely negative.

Cutaneous tests performed with stock proteins of *Streptococci* (three types), *pneumococci* (three types) *Micrococcus catarrhalis*, *B. coli*, *M. tetragenus*, *Staphylococcus aureus*, *albus*, and *citreus*, and an intradermic test with stock gonococcal vaccine were all negative.

Mr. Zamora reported that the tonsillar remains were a possible source of infection, but he was doubtful whether they were sufficient to account for the urticaria. The position was put to the patient and she decided to have the tonsils completely enucleated. The operation was performed immediately; an opportunity being also taken, while the patient was under the anæsthetic, of again examining the pelvis, with negative result. There was considerable hæmorrhage from the throat some hours after the operation, but this was controlled. Some days afterwards an attack of urticaria with swelling of the face and buccal mucous membrane developed, but rapidly subsided, and the patient went away to the sea to convalesce.

Since then there has been no recurrence whatever of urticaria and no febrile attacks. The patient has put on weight considerably and states that she is in better health and condition than she has been for years. All she complains of is a tendency to flushing of the skin of the face and neck when excited, but this is obviously merely a patchy erythema of psychical origin common in women of a certain temperament.

The enucleated tonsillar remains were examined bacteriologically, but only a few colonies of *Staphylococcus aureus* were obtained. It was subsequently found, however, that the incubator was out of order, and that the temperature rose to 42°–46° C. Later swabs were examined from the tonsillar beds, and a long-chained non-hæmolytic *Streptococcus*, together with a *Streptococcus brevis* and *Staphylococci* were obtained.

Comments.—This case is, perhaps, less convincing than Case III, and yet, in spite of the most careful search, no other

source of infection but the scarred tonsillar remains was discovered, the tonsillar glands were enlarged and became periodically swollen and tender, there was a history of rheumatic infection, and removal of the tonsillar remnants has not only led to a cessation of the urticarial attacks, but has been followed by great improvement in the patient's general health.

Case V.—Miss M. C., aged 31, came to see me in April of this year for chronic urticaria, with attacks of swelling of the eyes and lips, dating from an acute attack on New Year's Eve. She had had pneumonia of the right lung at Christmas 1920, and was subject to frequent colds and sore throats. During the air raids her thyroid gland became swollen, but later subsided. She complained of being easily tired. Changes in her dietary had had no apparent influence on her urticaria. On examination there were numerous urticarial wheals chiefly on the chest, abdomen, and thighs. The face and neck were flushed, there was no exophthalmos, the thyroid gland was rather full, the pulse-rate was 114, and there was obvious hyperidrosis of the face and hands. There were no signs of organic disease of the heart and lungs, though the heart-beat was rather tumultuous, and abdominal examination was negative. *The teeth* were in good condition; three were false. *The throat* was acutely inflamed, the anterior pillars of the fauces were injected, and there were yellowish patches on the posterior pharyngeal wall. *The tonsils* were swollen, injected, and contained septic material. There were neither symptoms nor signs of nasal sinus infection. I advised the patient to see Mr. Mollison, who thought enucleation of the tonsils advisable. He operated in May. Ten days after the operation she had a mild outbreak of urticaria on her face and chest, and another slighter one a fortnight later. Since then she has been entirely free from her eruption. The left side of the thyroid gland is, however, now considerably enlarged, and the flushing, tachycardia, and hyperidrosis are still evident. It is probable that this unilateral enlargement is adenomatous, and the patient has been advised to seek expert advice for its treatment. The enucleated tonsils were not examined bacteriologically in this case.

In all probability the infecting organism responsible for the urticaria in all these cases was a streptococcus longus, but it must be remembered that *B. coli* infections, *e. g.* pyelitis and cholecystitis, may produce urticaria, and the following case shows that a *Staphylococcus aureus* may provoke an urticarial reaction, should sensitisation to it occur :—

Case VI.—Miss C., a middle-aged lady, was referred to me by Dr. Mutch, under whose care she was for chronic rheumatism.

Some time previously she had had a large carbuncle on her left thigh, which had left a scar of considerable size. Shortly afterwards she began to develop crops of boils at intervals, chiefly around the vulva and perinæum. *With each fresh crop of boils a ring of urticarial wheals would appear around the scar of the carbuncle;* so constant in its conformation and development was this urticarial reaction that the patient termed it her "fairy ring."

It would seem clear that the area of skin at the original site of the carbuncle had become sensitised to the *Staphylococcus aureus*,—probably some active organisms were still present in the scar,—and that with each fresh infection in the form of boils a localised urticarial response occurred in the sensitised area. Treatment with an autogenous staphylococcal vaccine was successful in bringing about a cure of the boils, and the urticarial ring ceased to appear.

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WANT OF APPETITE AND REFUSAL OF FOOD IN CHILDHOOD

By H. C. CAMERON, M.D., Physician in Charge of the Children's Department, Guy's Hospital.

To-DAY, among children, disorders of appetite are encountered with too great frequency. It may be worth while to analyse the factors which are commonly at work in causing refusal of food, in the hope that from this study we may deduce some hints which may prove of value in treatment.

It is not part of my purpose to consider the close dependence of appetite in childhood upon the state of the physical health. Compared with the adult the child has so great a need for food that appetite and digestion are relatively prominent functions, and their disturbances make up a great part of the symptomatology of disease in the first years of life. For example, infective disorders of the most various types are apt to manifest themselves by symptoms referred almost wholly to the gastro-intestinal tract. Often indeed the disturbance of digestion is so prominent that the underlying infection remains unsuspected, and we are apt to find that cases of pyelitis, influenza and otitis media have been regarded as of a purely gastro-intestinal nature. Further, it goes without saying that in infancy, no less than in later life, confinement to close and overheated rooms, excess of clothing, and lack of exercise are capable of causing failure of appetite and refusal of food.

I propose, however, to deal only with cases—and to-day they seem especially frequent—in which there is nothing greatly amiss with the physical condition or with the physical surroundings of the child, and in which it is clear that the fault is one of management and control.

No one who is familiar with the ways of little children is likely to disagree that functional nervous disturbances of all sorts are more easily produced in early childhood than at any other time of life, and that of these a very large part is concerned with the sensitive alimentary tract. Functional disturbances which in adult life are only to be found in persons labouring under great mental strain or possessed of a grossly unstable mental constitution, among children are so common as to excite com-

paratively little attention. Thus, for example, violent fits of crying and emotional excitement, enuresis, pollakiuria, stammering, tics of all sorts, chorea, night terrors, clownism, mutism, pica, bulimia, etc., are of more frequent occurrence and of much less serious import in early childhood than in later life. Similarly we encounter a refusal of food from purely nervous causes, a veritable anorexia nervosa.

During the War a young man was brought to me in a condition of extreme weakness and emaciation. It was said that he had always been a poor eater, especially when worried or ill in any way. Lately, since he had been called up as a recruit for the army, his appetite had become much worse, so that for the last six weeks he had apparently eaten nothing at all. A careful physical examination failed to show any disease in any part of the body. He was admitted to hospital for treatment, but before anything could be done he took his own life by setting fire to his bed. A young woman similarly affected left the nursing home in which her recovery had taken place, bearing with her five pounds which she had abstracted from the purse of the sister to whose influence she chiefly owed her recovery. The suicide and the theft here testify to the instability of mind of which the refusal of food was a further symptom. Although not unknown, neither suicide nor theft is common in childhood as an indication of nervous disorder. Nevertheless the conduct of children in whom appetite has failed in this way is seldom normal in all other respects. Combined with refusal of food we find as a rule some other fault of conduct. The child so affected is commonly quick, forward and sensitive. Often he is an only child, living his little life in a community of adults. Always he is surrounded by the devoted care of his parents, who cannot hide from him the dismay and apprehension which his abnormal conduct excites. It is as a rule possible to appreciate that there exists a too intimate contact between the parents and the child, a contact which has sapped the vitality of the child and produced clear signs of nervous exhaustion and irritability. The too great care of his parents has enveloped him as it were with a cage, which shuts him off from all the stimulating forces of his environment, and like the caged animal, which in its carefully tended life must cease to exercise its natural powers, to build its home, to find its food, to care for its young, and even to procreate its species, he gives daily proof of perverted appetites and abnormal conduct. The symptom of refusal of food is an indication that the management of the child is at fault. Only by correcting the fault of management can the symptom be overcome. It is through the mother and by her means alone

that success can be achieved. A free and frank discussion with her of all the difficulties of the situation is necessary. In my experience after such a discussion a very large proportion of educated and understanding mothers appreciate the points at issue and are able then and there to overcome the difficulty.

In the production of this refusal of food of nervous origin it is possible to recognise the play of several forces. In some, especially in very young children just passing from the milk diet of infancy, the refusal is due to timidity and to a too great sensitiveness to new and strange flavours, or it may be to a want of dexterity in the mechanical work of mastication and swallowing the bolus of solid food. In others the refusal is in great part due to a restless negativism which impels the over-stimulated and restless child to make counterstrain against any traction which is exercised upon him. In others again unwise suggestions derived from the grown-up people around him are to blame, while in other cases the desire to tyrannise over his elders is predominant. Let us consider each of these factors in turn in some detail.

(1) Refusal of Food from Timidity or from Want of Dexterity in Mastication

An undue sensitiveness to the flavour of food is apparent with some infants at a very early age. Even with placid and well-managed children, at the time when the milk diet is being replaced by the mixed diet of the second year, we can often detect a start of surprise as a new flavour strikes the palate, or when unexpected sensations of hardness are first encountered. Especially in infants who are backward in all acts requiring muscular co-ordination, in infants who walk and talk late, we are apt to find the power of masticating and swallowing the more solid articles of food ill developed and slow to appear. The solid particle of food may be retained for long in the mouth and subjected not to mastication but to a kind of suction. Attempts at swallowing may give rise to coughing and choking. In the treatment of all such cases the conduct of the mother and nurse is of great importance. The child must be allowed time to become familiar with the new sensation, and to acquire the necessary dexterity. If he is hurried, if the spoon is plied too busily by the nurse, with many urgings and appeals, the self-confidence of the child is apt to be destroyed. His want of dexterity in using the spoon himself forces upon him a too passive rôle. His difficulty in masticating and swallowing makes him apprehensive of a process over which he has but little control. He becomes timid and shy about the whole business

of food. He will not experiment, or practise the new art of taking solid food. At the worst the approach of the uplifted spoon may produce a paroxysm of refusal and crying. In practice it is not uncommon to meet with cases of this sort. Their origin is comparatively simple. The timid, shrinking child, backward and faulty in neuro-muscular control, apprehensive of the whole performance, finds himself pitted against a strong-minded mother or nurse, who, grasping the spoon, is determined that the appropriate amount shall be administered.

Treatment.—We must see to it that as soon as possible the child himself controls the intake of food. If the difficulty seems to concern the flavour of the food, the child must be allowed to accustom himself to it. Fingers may be dipped in the egg or bacon fat or fruit juice, and the natural instinct to sense and explore will assert itself, if for a little the mother with her spoon betakes herself to the far end of the room. Similarly if meat is refused, as it often is because of its strong flavour, it is best to cut a long strip and allow the child, holding it in his hand, to suck it as he pleases. If left to himself, so that he feels master of his actions, he will soon fall to exploring the situation, and in a short time it will be clearly apparent that pleasurable sensations predominate. When the difficulty appears to concern the consistency of the food rather than the flavour, when chewing and swallowing the solid bolus appears impossible, it may be necessary to thicken the milk with gelatine or cornflour in the endeavour to achieve some gradation between the fluid diet and these too difficult solids. Since this difficulty is specially occasioned by a want of neuro-muscular control, it is important that free movement of all sorts should be encouraged. As hands and feet gain dexterity we may be confident that this difficulty will rapidly disappear. Refusal of food from this cause is common in children who have been bedridden for any reason. In infants with diplegia, who are unable to control the movements of their stiff spastic limbs, it is the rule. We must do all that we can to encourage precision of movement. The mechanical difficulty of dealing with the bolus after its introduction into the mouth is not likely to survive the moment when the child becomes able himself to use a spoon and control the intake.

(2) Refusal of Food from "Negativism"

In young children of a certain type we find restlessness and irritability showing itself in "negativism," in an apparently invincible determination to do the opposite. Shepherded in one direction, the child shows his determination to proceed in the

other. Dressing equally with undressing, going upstairs no less than going down, are resisted and fought against. Such conduct in general is only found in children who are directed and controlled too much, and upon whom their elders exercise a too constant and obvious traction. With some mothers and nurses reproof, appeal and expostulation, all alike futile and without effect, succeed one another unendingly the whole day long. With such handling many children seem impelled to keep straining in the opposite direction. Refusal of food is often a symptom of this opposition and negativism.

Among the children of the very poor, to whom the price of food is a main consideration, it is interesting to note how often this negativism shows itself in a huge and apparently insatiable appetite. Driven away from the cupboard with threats or entreaties by their harassed mothers, they return clamouring again and again. With the children of the well-to-do, maternal traction almost always takes the form of a too constant and urgent invitation, and their response characteristically is that of persistent opposition and refusal. That which is doled out grudgingly and unwillingly is taken greedily, that which is pressed upon the child with appeals and entreaties is refused.

Treatment.—When refusal of food is for the most part an act of negativism, the symptom is not difficult to control. The suggestion with which all food is proffered must be altered. The mother must manage to convey to the child that the one thing she is determined upon is that he shall not take too much. If there is sufficient show of reluctance, if helpings are haggled about and when opportunity occurs refused altogether, the child whose refusal is due to negativism can be made clamorous for food as easily as he can be made to refuse.

Meanwhile it is necessary that the management of the child should be radically altered. Negativism is a symptom of nervous unrest. It is seldom in early childhood that nervous unrest is the result of any particular emotional shock, trouble or anxiety. It is more often a sequel of infective illness or an accompaniment of any considerable nutritional disturbance. Equally often, by a sort of summation of stimuli, it is due to the combined effect of many petty emotional outbursts. An extreme sensitiveness to the personalities of those who are in charge of him and of the details of his little life is the mark of the nervous child. With some people, as we say, the children are always good. With others, perhaps equally fond of children, their conduct at once deteriorates. Those who succeed, in general proceed without too many commands, appeals, expostu-

lations and threats. They go on their way confident that the children will conform. They do not appear ever to contemplate refusal. They throw out no challenge to the child, they do not seem to exercise any obvious traction upon him. With such a hand on the rein, negativism does not appear. It grows only with reproofs and expostulations to which the child has become habituated and for which he cares nothing. It will persist until all this is changed. Negativism shown both in refusal of food and in a hundred other actions in the day is a symptom of nervous unrest in a child in whom attempts at control, while constant and conspicuous, are yet ineffectual.

(3) Refusal of Food from Faulty Suggestions

The little child has no power of self-analysis. He has no knowledge of his own individuality apart from ideas derived from the grown-up persons around him. Conceptions and beliefs concerning him which become rooted in the minds of too apprehensive or pessimistic parents have great power to influence his conduct. In accordance with the reputations which become attached to him in the household, the child moulds his conduct. For instance, it may not occur to him to doubt that he is a little boy of whom it is characteristic to sleep well and soundly, to be particularly regular in the daily action of his bowels, and to have no fear of animals. Such helpful suggestions have been made to him constantly and he has not failed to respond to them. His parents take great delight in these good qualities. In regard to them they have been encouraging and optimistic. All the stress has been laid upon the child's success, to his occasional failure less attention has been paid. But in this one respect of appetite and the intake of food the position may be reversed and the suggestions which proceed from the parents to the child may be persistently harmful. The over-anxiety of parents naturally tends to concentrate upon the sensitive alimentary system. For instance, a mother who has seen her child in the first year of life fail to thrive, and become wasted and marasmic, may never again be able to deal with the proper lightness of touch with all matters that concern the child's food. As regards this one point she is nervous, timid and apprehensive. In all other respects the child may be braced and strengthened by her. The daily action of the bowels, the control of the bladder, the nightly sleep, may all be firmly established because in these matters she feels herself confident of success. In the matter of food she feels powerless. Even if no word is said, the child is very conscious of the atmosphere of distress and worry which envelops the whole household. Too often the most harmful

suggestions are made openly in speech before him. To the child it seems as if it was upon this one aspect of his life that the attention of the whole household is concentrated. It is confidently said of him that he has no appetite, or that he will not eat this or that article of food, or that the only thing he can be got to take or that his stomach can be induced to tolerate is the outside of sponge-cakes. When such remarks as these are repeated day by day by nurses and mothers, uttered with the most profound conviction, the force of such suggestion upon a little child becomes immense.

Treatment.—It is not enough to rest content with omitting harmful suggestions. Every day and many times in the day there must be comments on the remarkable change which is beginning to be apparent. Day by day it is noted with satisfaction many times in the child's hearing that he is eating better and better. The whole household, previously so pessimistic, now takes delight in the increasing appetite. Nurse shouts the good news from the nursery door. There is quite a rush to be the first to tell the father in the evening. Soon the child, equally pleased with his new reputation, will proclaim to all that he " eats everything."

(4) Refusal of Food and the Instinct of Self-Assertion

In general the child is very conscious of the stir which his refusal occasions. By refusal he knows that he can dominate nurse and mother and make all his little world revolve around him.

A boy of three years of age was brought to me by his parents in a motor-car. On the arrival of the car to take him on board, he was reported to have said at once, " Not eat my dinner," a remark which appeared at first sight inexplicable. It appeared, however, that some three weeks before the same car had been hired to take him to his grandfather's for midday dinner. This he had completely refused. His grandfather and grandmother had joined in the fray. Clearly the recollection of the time thus spent had lived in his memory not unpleasantly, so that when the car again appeared he hopefully anticipated a return of the encounter. In bad cases conduct of this sort may be repeated day after day. Every meal-time becomes a signal for struggling and tears. Often the emotional disturbance inhibits the digestive activity and vomiting or abdominal pain follows the meal.

Treatment.—When the refusal of food appears to arise mainly from a desire on the part of the child to gratify his own sense

of self-importance, it can only be overcome if the mother and nurse are able successfully to assume an air of complete indifference. It is no easy task, at least for the mother. It is because the child knows so well that she does care, that he is confident of the success of his tyranny of tears. This sure ground of confidence must be knocked from under his feet once and for all.

In any one case of persistent refusal of food these different factors are combined in varying proportion. An intimate conversation with the mother will generally enable us to determine the lines along which cure shall be attempted. Treatment by modification of the diet has little effect, and has the notable disadvantage of encouraging the over-anxious mother to believe that certain common and ordinary articles of food are capable of producing the most disastrous results in her child. If such is her belief, it is likely that her apprehension will not be without influence on the child, and will tend to render a sensitive digestion still more sensitive. Treatment by tonics, alkalies, acids or bitters is without effect, except only as these serve to encourage a despairing mother. The attitude of the child towards its food extends to and involves gastric secretion and gastric movement. Digestion and nutrition will not improve until the child is straining towards its food, not recoiling from it. All the most striking successes in the treatment of disorders of this sort which I can recall have followed upon a long and intimate talk with the mother, in which the fault of management has been explored and made plain. An alteration in the management of the child in the essential particulars produces the happiest results.

OCCULT BLOOD IN THE FÆCES

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SINCE Boas,[1] in 1901, first directed attention to the importance of the chemical reactions for occult blood in the fæces in disorders of the alimentary tract, these tests have been employed with increasing frequency, and are now in more or less general use in the routine investigation of gastro-intestinal affections.

Leech,[27] in 1907, made the first English contribution on the subject, and his excellent and exhaustive thesis merits careful consideration.

The tests have proved misleading, however, in the experience of many clinicians and are apt to be regarded with suspicion. Particularly is this the case when they are employed during the medical treatment of gastric and duodenal ulcers to indicate a suitable time for changing the patient's diet in accordance with the stage of healing of the ulcer. There is an increasing likelihood that ultimately no reliance will be placed upon this diagnostic and therapeutic aid. The variety of tests which have been advocated and the numerous modifications in their technique contribute largely to this unsatisfactory position.

A reliable standard clinical method of examining the fæces for occult blood is undoubtedly needed. It must be sufficiently simple and free from fallacies to enable the ordinary observer to obtain helpful information. At present probably every biochemical laboratory has its own routine method of performing this examination which is considered satisfactory, and the danger of adding still further to the confusion by another contribution to the copious literature is not to be ignored.

The results of my investigations and the conclusions drawn from them are brought forward for the light they throw on the relative merits of some of the tests most commonly employed.

The prefix " occult " should be restricted to blood which is unrecognisable as such by the naked eye, and only detected by special chemical or spectroscopic methods. The blood in the fæces associated with hæmorrhoids is thus rarely occult, as it appears visibly on the surface of the stool; nor are the well-marked cases of melæna, for " altered " blood is not necessarily

occult blood. It is of interest to note that Barker [2] states that even 5 per cent. of blood in the stool may pass unnoticed by the naked eye.

This investigation has been carried out upon hospital patients who were presumably normal as regards their gastro-intestinal tracts, and upon others who had definite disease of the alimentary system. With the former the various sources of bleeding which might interfere with the results of the tests were excluded as far as possible, and the cases examined may fairly be taken as reliable normal controls. The patients were medical and surgical ward cases at Guy's Hospital and Lambeth Infirmary.

Methods

The tests for altered blood in the fæces are very numerous, and their modifications even more so (e.g. *inter alia* [3-17]), but for practical purposes the benzidine and guaiacum tests are the two great rivals. In the case of the former the Schlesinger and Holst [5] technique and in the case of the latter Weber's method [3] originated by him in 1898 in order to eliminate those substances which interfered with the original guaiacum reaction of Van Deem, are perhaps employed most frequently.

In the series of " normals " the following tests were used in each case in the manner detailed.

1. *Benzidine test.*—A small amount of fæces is thoroughly stirred in water to form a thin paste and boiled for two minutes, allowed to cool, and then diluted with an equal quantity of distilled water. A few drops (3–10) of this emulsion are added to 1 c.c. of a concentrated solution of benzidine in glacial acetic acid, and the two are well mixed by shaking; then 3 per cent. hydrogen peroxide is carefully added until a blue or green colour develops, or until about 2 c.c. of peroxide have been used, the shaking being continued throughout.

The benzidine used was Merck's (Darmstadt) Benzidin. puriss., other preparations being reputed to give unreliable results.

2. *Guaiacum test.*—A portion of fæces about the size of a walnut is thoroughly stirred with 8 to 10 c.c. of glacial acetic acid. To the emulsion is added slightly more than an equal quantity of ether, and the mixture is again thoroughly stirred. By using these amounts sufficient acid-ether extract is obtained for the spectroscopic examination as well as for the guaiacum test. To about 2 c.c. of this acid-ether extract are added 5 drops of freshly prepared tincture of guaiacum, and then slowly 10 per cent. ozonic alcohol (10 c.c. 20 vol. H_2O_2, alcohol to 100 c.c.),

ether, or turpentine until a blue or green colour develops or excess has been used.

3. *Phenolphthalein test.*—Full details of the technique of this test, which was advocated by Boas, will be found in *Fæces of Children and Adults*, by P. J. Cammidge (p. 184), whose description has been followed.

4. *Spectroscopic examination.*—The acid-ether extract as prepared for the guaiacum test is utilised. Apart from the bands of stercobilin and chlorophyll those of hæmatoporphyrin and acid hæmatin are sought. When the source of blood is high up in the alimentary tract the gastric, duodenal or intestinal juices destroy the red corpuscles, the hæmoglobin being converted into hæmatin, which in turn is partly or wholly converted into hæmatoporphyrin, an iron-free derivative. When the bleeding occurs in the rectum or anal canal, hæmatin may, but hæmatoporphyrin will not, be found. Acid hæmatin bands, if present, will be seen on adding an equal quantity of 10 per cent. hydrochloric acid to the acid-ether extract and shaking well; they are in the upper layer of the mixture. Only when the blood is present in considerable quantity are these acid hæmatin bands seen, the spectroscope being a much less delicate test than the chemical colour reactions.

It was considered that no useful purpose would be served by employing any of the other tests for occult blood.

A. "Normal" People on Ordinary Diet

The above four tests were carried out upon sixty "normal" patients whilst on ordinary hospital full diet with the results shown in Table I.

TABLE I.

A comparison between the tests employed in examining the fæces for occult blood of sixty normal people on ordinary diet.

Test.	Positive.		Feeble-Positive.		Negative.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Benzidine . . .	42	70·0	11	18·3	7	11·6
Guaiacum . . .	15	25·0	23	38·3	22	36·6
Phenolphthalein. .	35	58·3	11	18·3	14	23·3
Spectroscopic . .	0	0	0	0	60	100·0

Benzidine test.—In my experience this was most satisfactorily carried out as a "ring" test, the hydrogen peroxide being gently added, the change of colour first appearing at the junction of the

two liquids. A positive reaction was taken to be one in which a deep blue or purple colour rapidly appeared; a faint purple, bluish, or greenish tint was interpreted as a " feeble-positive."

Guaiacum test.—A positive reaction was one in which a blue or deep green colour resulted, a feeble-positive reaction when a faint greenish tinge appeared. If a clear blue or violet colour is taken as the standard for a positive reaction, as White,[18] Schumm,[19] Coope,[20] and others insist, then quantities of occult blood even large enough to be visible with the spectroscope as hæmatoporphyrin will be overlooked. Some may claim that this enhances the practical value of the test, but the experiments on ingested blood overthrow such a view. The resulting dilemma is a strong argument against the guaiacum reaction.

Phenolphthalein test.—This test was not used in the subsequent investigations, for it possesses several practical disadvantages. The reagent must be frequently renewed, as unless freshly prepared it is unreliable. The details of the test must be carried out with extreme care, otherwise equivocal results are obtained, and altogether the test would seem to possess no advantages unless its great sensitiveness be so considered. Even ordinary tap-water has been found capable of producing a positive reaction. It is certainly unsuitable as a routine method.

Spectroscopic test.—The only bands seen were those of chlorophyll and stercobilin, the hæmoglobin derivatives being consistently absent. The explanation is that hæmatoporphyrin and, to an even greater extent, acid hæmatin bands are only present when meat is taken in large quantities, certainly larger than is present in the ordinary hospital full diet.

Hektoen, Fantus and Portis [16] reported positive benzidine reactions in 90 per cent., and positive guaiacum reactions in 93 per cent., of a series of fifty-eight normal people on ordinary diet, whereas White [18] gives corresponding figures of 100 per cent. and 20 per cent. The discrepancy between these figures and the present findings would appear to be largely due to the different techniques employed in these tests, and also, to some extent, to the variability of the diet classed as " ordinary."

In this series a definite blue colour with the guaiacum test was seldom obtained, in contrast to the usual strong prussian-blue colour with the benzidine test. The majority of the benzidine reactions classed as " feeble-positives " would have been interpreted as frank " positives " when employing the guaiacum test. It is well known that the same standard of colour change demanded of the benzidine test is rarely reached by the guaiacum test; the latter will show much less alteration in colour than the former with equal amounts of blood.

These figures clearly show that the guaiacum test is inferior in delicacy to both the benzidine and phenolphthalein tests, and the spectroscope is the least sensitive of all.

B. "Normal" People on Hæmoglobin- and Chlorophyll-free Diet

The same "normal" people were then given a diet containing no meat, meat extractives, fish, soup, coloured vegetables or fruit. By this means extraneous sources of hæmoglobin and chlorophyll were excluded, the actual diet consisting of milk, milk foods, potatoes, and bread and butter. All green or coloured vegetables and fruit contain chlorophyll or its chemical analogues and are therefore to be avoided. Since the above experiments were made I have examined a variety of vegetables and fruits, both raw and cooked, and find that the following are chlorophyll-free, or at any rate the amount present is too small to be a source of error in these tests, and so may be allowed during the period of restricted diet:—potatoes without "jackets," cauliflower (head), boiled onions, white (Jerusalem) artichokes, young parsnips, young celery, bananas, pears without skins.

A preliminary thorough emptying of the colon is essential, and may be obtained by enemata or saline aperients according to the individual requirements. This is carried out in order to remove as completely as possible all hæmoglobin-containing contents of the colon and rectum which adhere to the walls.

Powdered charcoal was used as a means of distinguishing the stools of various periods. Rapin [21] states that charcoal acting as a catalyser can produce positive reactions with the various chemical tests, but I am unable to confirm this, and am convinced it was not a source of error. A tablespoonful of powdered charcoal was given in milk with the last ordinary full-diet meal at night, and the restricted diet commenced the following day. Another tablespoonful was given with the last meal of the restricted diet. Discarding the first black-coloured stool, a specimen of each subsequent motion was obtained up to, and including, the second black stool. These specimens were examined for occult blood by means of the three methods already described.

Owing to the varying rates of progress of the intestinal contents, the specimen which first gave negative results varied. In some cases negative results to the three tests were obtained with the stool passed after only one day's dieting, more often it required the full three days, and in eleven (18·3 per cent.) of the cases a feeble-positive guaiacum reaction was still present after three days' dieting, although, curiously enough, the other

tests were negative. Thus in 81·7 per cent. of the cases negative results to the benzidine, guaiacum, and spectroscopic tests were obtained after three days of strict diet.

After four days of this diet the guaiacum reaction was negative in every case, as also were the benzidine and spectroscopic tests.

TABLE II.

A comparison between the tests employed in examining the fæces for occult blood of sixty normal people on a hæmoglobin- and chlorophyll-free diet.

Dietary period.	Test.	Positive.		Feeble-Positive.		Negative.	
		Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Three days	Benzidine	0	0	0	0	60	100·0
	Guaiacum	0	0	11	18·33	49	81·66
	Spectroscopic	0	0	0	0	60	100·0
Four days	Benzidine	0	0	0	0	60	100·0
	Guaiacum	0	0	0	0	60	100·0
	Spectroscopic	0	0	0	0	60	100·0

C. "Normal" People on Hæmoglobin-free Diet

The effect of chlorophyll-containing foods upon these tests was then investigated in twenty-six of the above cases. At the end of the period of strict dieting as described, green vegetables and fruit were added, but meat, fish, and soups were still withheld.

Table III. shows the results obtained.

TABLE III.

A comparison between the tests employed in examining the fæces for occult blood of twenty-six normal people on a hæmoglobin-free diet.

Test.		Positive.		Feeble-Positive.		Negative.	
		Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Benzidine		0	0	0	0	26	100·0
Guaiacum		0	0	5	19·2	21	80·7
Spectroscopic	Hb derivatives .	0	0	0	0	26	100·0
	Chlorophyll .	24	92·3	0	0	2	7·6

It is noteworthy that in one-fifth of the cases a feeble-positive guaiacum reaction occurred, whereas the benzidine test was

uniformly negative. The colour-reaction in these five cases was a slight change from definite yellow-brown to green-brown. With regard to the spectroscopic examination the bands of chlorophyll were obvious in all but two cases.

The inclusion of chlorophyll-containing substances in the diet is a potential source of error when the guaiacum test is used, and it is probably safer to omit them altogether even when the benzidine test is employed.

Clark[23] found that green vegetables may cause both the guaiacum and benzidine tests to be positive. Furthermore, it has been stated that the absorption bands of chlorophyll and hæmatoporphyrin occurring together resemble, to a certain extent, those of acid hæmatin, and so might mislead as to the amount of blood present.

In relation to this, the chemical connection between hæmoglobin and chlorophyll through their porphyrin constituents, and the fact that a compound obtained from chlorophyll has been reputed to give the same absorption spectrum as hæmatoporphyrin derived from hæmoglobin, are of no little interest.[22]

D. Pathological Cases

An indiscriminate series of fifty medical cases with gastro-intestinal disorders, comprising amongst others gastric ulcer, duodenal ulcer, carcinoma of stomach, gallstones, ulcerative colitis, and cirrhosis of liver, was then investigated.

No disease was represented by a number of cases sufficiently large to enable any reliable deductions being made, nor was this the object in view. The series was utilised as a further means of comparison between the already mentioned tests, in cases where the occult blood was of endogenous origin.

The results shown in Table IV. were obtained.

TABLE IV.

A comparison between the tests employed in examining the fæces for occult blood of fifty cases with various gastro-intestinal disorders.

Test.	Positive.		Feeble-positive.		Negative.	
	Cases.	Per cent.	Cases.	Per cent.	Cases.	Per cent.
Benzidine	27	54·0	3	6·0	20	40·0
Guaiacum	21	42·0	12	24·0	17	34·0
Spectroscopic { Hæmatoporph. .	14	28·0	0	0	36	72·0
Spectroscopic { Acid hæmatin .	3	6·0	0	0	47	94·0

E. "Normal" People with Ingested Blood

Ten individuals with normal alimentary tracts were given a diet containing no hæmoglobin. After the stage of negative occult blood reactions was reached, 1 c.c. of their own blood withdrawn from a vein was given by mouth in a single dose mixed with the food, and the stools subsequently examined for occult blood.

In every case a deep blue colour was obtained with the benzidine test, and a positive reaction, varying from blue to deep greenish-blue, with the guaiacum test, while the spectroscope showed the bands of hæmatoporphyrin and acid hæmatin in seven cases.

The stage of negative reactions to all tests having been again reached, 0·5 c.c. of blood was given as before. Examination of the stools on several subsequent occasions gave the following results. The benzidine test was negative in seven cases and gave a feeble reaction in three cases, the guaiacum test was negative in nine cases and gave a feeble reaction in one case, while the spectroscopic test was negative in every case.

Thus the smallest quantity of blood given by mouth in a single dose which will produce a positive benzidine reaction in the fæces is between 0·5 c.c. and 1 c.c. The amount necessary in the case of the guaiacum reaction is about 1 c.c., and in the case of the spectroscope 1 c.c. or more.

Abrahams [24] found that not until 1 c.c. of blood at one dose was taken could there be certainty of a positive benzidine reaction.

Severe gingivitis and inflammatory conditions of the nasopharynx are undoubtedly potential sources of error in occult blood investigations, for it is quite possible that 1 c.c. of blood could be swallowed within a comparatively short time. Minor degrees of the above conditions can hardly be held responsible for erroneous results.

Discussion

A comparison between the results shown in Table I. and Table IV. illustrates several points. It will be observed that in the series of normal cases the benzidine reaction was positive in 70 per cent. of the cases, whereas the guaiacum reaction was positive in only 25 per cent., and that in the series of pathological cases the corresponding figures were 54 per cent. and 42 per cent. So far this is no more than a confirmation of the well-established fact that the benzidine reaction is more sensitive than the guaiacum reaction, although Vaughan [12] states that he

found positive benzidine reactions were almost invariably accompanied by positive guaiacum reactions.

The probable reason for the greater divergence of the percentages in the normal series is that the amounts of occult blood present were much smaller than in the pathological series, in fact so small in many cases as to produce no definite positive reaction with the guaiacum test.

The percentage of feeble-positive results obtained with each test shows how frequently this unsatisfactory finding occurs with the guaiacum as compared with the benzidine test, the pathological cases illustrating this most strikingly. The colour changes obtained with the benzidine test, as already stated, are much clearer and sharper than those occurring in the guaiacum test; hence the fewer indefinite results obtained with the former reaction.

The criticism that the benzidine test is too sensitive for clinical purposes is not supported by the results obtained from these experiments. The Schlesinger and Holst [5] modification was especially designed to overcome this real defect of O. and R. Adler's [25] original test, and appears to have done so most satisfactorily.

The benzidine reaction is therefore preferable to the guaiacum reaction as a test for occult blood in the fæces for the following reasons :—

1. The colour change is more obvious and less liable to misinterpretation, especially when small amounts of blood are present.

2. It reacts to smaller quantities of occult blood by a definite colour change, and, when used in the manner described, does not react to negligible quantities.

3. The technique is simpler and fewer reagents are required. Reliable results are more readily obtained.

4. A negative result has a greater significance and value than in the case of the guaiacum reaction.

The spectroscope is of great assistance when the bands of hæmatoporphyrin or acid hæmatin are obtained, for this demonstrates conclusively the presence of blood. Furthermore, it removes all doubt that the blood found may have been introduced in the diet.

A special note with regard to the use of occult blood examinations during the course of medical treatment of gastric and duodenal ulcers is necessary. It is customary for the patient to be subjected to a strict dietetic treatment until several consecutive negative occult blood reactions are obtained. This is no doubt an excellent precept, but in practice it is sometimes found

that after many weeks, although the ulcer appears to have completely healed, there still apparently remains a little occult blood in the fæces. As Abrahams [26] says, "it is not the negative result in occult blood examinations but the feebly positive which causes misunderstanding." Particularly is this the case when the guaiacum reaction is employed; but it is rarely so with the benzidine reaction used in the manner described. If, when even the latter test is used, such an impasse is reached, the clinical and x-ray evidence must override the feeble-positive occult blood reactions, and the stage of more liberal diet commenced.

Routine Method Advocated

1. A diet free from hæmoglobin and chlorophyll, but permitting the vegetables and fruits detailed, is given for a minimum period of four days. A charcoal biscuit is given with the last ordinary meal prior to commencing the restricted diet.

2. Iron compounds and iodides must not be administered during the investigation, and extraneous sources of hæmorrhage must be searched for and eliminated.

3. The bowels are kept open daily during this period, if necessary, by the use of saline aperients or enemata.

4. The first, and preferably the second, stool passed after the fourth day of dieting are examined, if the bowels have been adequately opened each day.

5. The benzidine test and the spectroscopic examination should be employed as described.

6. If, after brushing the teeth, there is any bleeding from the gums, the patient must rinse the mouth out carefully afterwards until every trace of bleeding disappears.

A positive benzidine reaction will then signify the presence of pathological occult blood, and a positive spectroscope examination will show it to be present in fairly considerable quantity. A negative benzidine reaction will prove the absence of occult blood in quantity of any clinical significance. A negative spectroscopic test, when blood visible to the naked eye is present, or when from the intensity of the positive benzidine reaction it is deemed present in considerable amount, would strongly suggest that the source of bleeding is in the anal canal or rectum.

In conclusion, I wish to thank Dr. A. F. Hurst for many helpful suggestions, Mr. J. H. Ryffel for his advice and kindly criticism during the investigation, and for permission to carry it out in his laboratory at Guy's Hospital, also Dr. G. H. Stebbing,

of Lambeth Infirmary, for his courtesy in placing many cases there at my disposal.

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LEPTOSPIRA ICTERO-HÆMORRHAGIÆ IN SURREY RATS

WITH NOTES OF A PROBABLE CASE OF SPIROCHÆTAL JAUNDICE FROM THE DISTRICT

By R. D. PASSEY, M.C., M.D., Griffiths Demonstrator of Pathology, and J. A. RYLE, M.D., Assistant Physician to Guy's Hospital.

SPIROCHÆTOSIS ICTERO-HÆMORRHAGICA has been recognised as world-wide in its distribution. In Japan it has been endemic, particularly among workers in wet mine-shafts.[1] During the war it became epidemic among troops on various fronts, and was especially prevalent at one period in British divisions holding the Ypres salient.[2] Small house-epidemics and sporadic cases of a febrile type of infective jaundice are also recorded in the literature, [3, 4] but most of these descriptions belong to a period before the discovery by Inada and his collaborators of the causal organism.

Both in Japan and Europe the rat has been proved to be the carrier of the infection. In Japan the leptospira was demonstrated in the blood or urine of 38 per cent. of field rats in an infected zone. In this country A. C. Coles [5] reported the presence microscopically of the leptospira in the kidneys of 9 out of 100 rats caught in the Bournemouth area, but this was not confirmed by animal inoculation. Foulerton [6] found the leptospira in 4 out of 98 rats (*Mus decumanus*) in the London area, but failed to find them in the few black rats which he examined.

Very few cases of spirochætal jaundice have, however, been reported in this country, and at the time of writing the only proved case is that described by Manson-Bahr [7] in 1922 of a man who acquired the disease a few days after immersion in the Thames. It is of interest that Martin and Pettit [8] reported a case in Paris following immersion in the Seine. Sir Humphry Rolleston has informed us of a case, referred to in his book,[9] which he saw at Weybridge in 1905. In 1919 a worker with refuse in Reading succumbed to an attack of infective jaundice terminating in coma; his wife, who also became infected, was admitted into Guy's Hospital under the care of Dr. A. F. Hurst. She was seen by one of us (J. A. R.), and the conclusion based

on the history and clinical features was that she and her husband had both suffered from spirochætosis ictero-hæmorrhagica.

We consider the case described hereunder to have been a further instance of a sporadic infection in this country. Infection occurred at Guildford, and rats from the same town were shown to harbour *Leptospira ictero-hæmorrhagiæ*. Believing that knowledge of the etiological and clinical features of the disease should be more widely disseminated, we have thought it worth while to describe this case and the experiments conducted in connection with it in some detail.

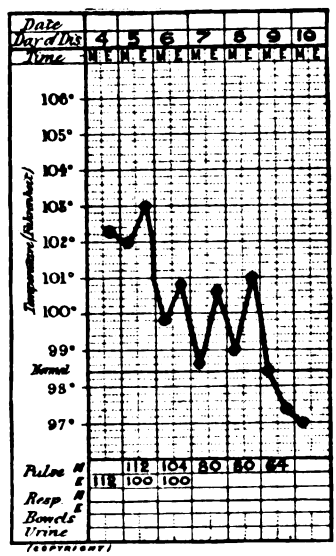

Fig. 1.—Temperature Chart of Sergt. B.

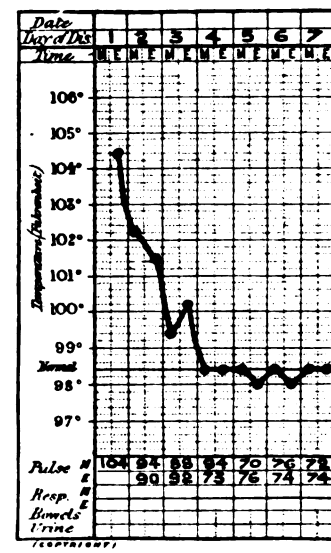

Fig. 2.—Temperature Chart of Mrs. H.

Mrs. H. was taken ill suddenly on April 6, 1922, with fever, headache and muscular pains. She developed a morbilliform rash and after about eight days became deeply jaundiced. Other symptoms included epistaxis, albuminuria on one occasion, conjunctival injection and stomatitis. The jaundice became very intense and persisted for several weeks.

On May 21, 1922, the patient was admitted into New Lodge Clinic under the care of Dr. A. F. Hurst for further investigation. She then still showed a deep orange-yellow jaundice, a definite enlargement of the liver, and a palpable but non-tender gall-bladder. Apparently there had been superficial abdominal soreness in the right upper abdomen in the early stages of the illness. Excepting for troublesome pruritus due to the jaundice and slight photophobia, the patient was free from subjective symptoms, and her appetite had begun to return. She had been afebrile since the third day of the disease. The urine was

alkaline and showed much bile-pigment, but no albumin, sugar, or abnormal deposits. Catheter specimens showed no spirochætes on dark-ground examination. The blood-serum was highly pigmented and gave a well-marked indirect reaction with Hijman van den Bergh's test. The fæces on May 18 had been reported as putty-coloured, but showed the presence of stercobilin. In the Clinic they showed a negative test for occult blood and stercobilin was present. They rapidly became definitely pigmented. Blood-sugar and urine diastase estimations gave normal readings. There was no appreciable anæmia, the hæmoglobin being 76 per cent. Injection of magnesium sulphate down a duodenal tube produced a free flow of bile, which contained no pus cells. Cultivations from the bile grew some Gram-negative bacilli, which proved to be lactose fermenters.

The temperature chart (Fig. 2) is reproduced in conjunction with that of a proved case under the care of one of us (J. A. R.) during the Belgian epidemic of 1917 (Fig. 1). The pyrexial curve is of shorter duration than was commonly the case in the Flanders epidemic; ten days usually elapsed before defervescence in this series.

In a previous paper by one of us (J. A. R.)[10] recounting the clinical features of the disease in a series of fifty-five cases, the ten most prominent symptoms and their percentage incidence were given as follows—

(1)	Jaundice	73
(2)	Albuminuria	58
(3)	Limb pains	49
(4)	Herpes	43
(5)	Vomiting	42
(6)	Conjunctival injection	40
(7)	Hæmoptysis	29
(8)	Acetonuria	16
(9)	Epistaxis	16
(10)	Abdominal pain	12

To these may be added (11) pyrexia, which probably occurs in the early phase in 100 per cent. of cases; (12) adenitis; (13) morbilliform rashes;[11] (14) other hæmorrhages; (15) photophobia; and (16) stomatitis, while (17) abrupt onset was so frequent that it may also be included among the characteristic features of the disease.

Of these manifestations the patient showed the presence of (1), (2), (3), (6), (9), (10), (11), (13), (15), (16) and (17).

The anomalous features of the case were the delay in appearance of the jaundice, which most commonly appears between the third and fifth days, the very considerable enlargement of the

liver and enlargement of the gall-bladder, suggesting some additional obstruction of the main bile channels, and the long persistence of deep jaundice, which may have been similarly accounted for. At no phase of the disease was there anything to warrant a diagnosis of gall-stones or cholecystitis, and there was, as later investigations showed, nothing indicating pancreatic disease. The case was clearly much too severe for a simple catarrhal jaundice, and it had none of the features of a hæmolytic jaundice. There had been no exposure to toxic agents known to produce hepatitis. Pneumonic and septicæmic bacterial infections could be excluded. Other forms of acute infective hepatitis with jaundice are practically unknown in this country. It seemed, therefore, that a diagnosis of spirochætosis ictero-hæmorrhagica might reasonably be entertained.

The patient was asked whether there were any rats in her house. It then transpired that at the time when she became ill a garage was being excavated on the adjoining premises, and that her garden, hen-house, and possibly other buildings, were literally over-run with rats. The Medical Officer of Health was appealed to for animals to investigate, but unfortunately by this time the rats had been exterminated in the immediate neighbourhood of the patient's house.

However, early in July three adult brown rats (*Mus decumanus*), which had been caught in Guildford, were kindly sent by Dr. Pierce, the Medical Officer of Health.

These animals were observed for fourteen days in the laboratory, during which time they appeared to be quite healthy. They were then killed and the kidneys of one rat were crushed and emulsified in saline solution by grinding with sterile sand in a sterile mortar. After standing, so as to allow the gross particles to settle, 2 c.c. of the emulsion were injected intra-peritoneally into a guinea-pig. The kidneys of the other two rats were then ground up in the same mortar together with the remains of the first rat's kidneys. The resulting pooled saline emulsion was injected into two other guinea-pigs by the intra-peritoneal route. The first pig survived; the other two succumbed, one on the seventh and the other on the ninth day, both showing marked jaundice. The one which died on the seventh day had a slight purulent peritonitis, which may have accounted for its earlier death. Emulsions of the liver and kidneys of these two animals were inoculated into three other guinea-pigs in each case. These animals all died with marked hæmorrhagic jaundice. Passage was made in all through eight groups of guinea-pigs, totalling thirty animals, and of these all except one died, showing the usual post-mortem appearance of spirochætosis ictero-

hæmorrhagica. That is to say, there was a varying degree of jaundice, often very intense; there were subcutaneous and retroperitoneal hæmorrhages, and the typical " butterfly " mottling of the lungs, as described originally by the Japanese. The only survivor developed a mild jaundice, from which it recovered completely.

The leptospira was demonstrated in many specimens of liver and kidney from these animals, both by a modified Levaditi method and by Giemsa's stain. Morphologically the appearances were undoubtedly those of the *Leptospira ictero-hæmorrhagiæ*.

In the middle of August some of the patient's blood was obtained, and two pigs were inoculated with 1 c.c. of liver emulsion from an animal dead of the disease together with 2 c.c. of the patient's serum in one case and 5 c.c. in the other. Three control pigs were inoculated: one with 1 c.c. of the emulsion alone, another with 1 c.c. of emulsion + 2 c.c. of normal serum, and the third with 1 c.c. of emulsion + 5 c.c. of normal serum. All five animals died. Thus the patient's serum in the above quantities failed to protect. We do not, however, feel that this militates seriously against the original diagnosis for the following reasons. Firstly, the patient at the time of this experiment had been convalescent for some four months, and the blood may therefore have lost much of its antibody content. Secondly, the liver emulsion may have been proportionately in too big a dose for the quantity of serum employed. Thirdly, it is probable that the virulence of the strain had been considerably increased by passage.

Conclusions

Ordinary English rats are known to carry the leptospira of spirochætosis ictero-hæmorrhagica. There is, therefore, a possibility of human infections whenever and wherever a close association of rats with human beings takes place. In the civil community epidemics are unlikely to occur, but there is always a possibility of sporadic or house-infections.

In Japan the disease is reported as having a mortality of 30 per cent. Among the British troops in Flanders the mortality was 5 per cent. The disease is a serious disease and in the acute phase causes much suffering and prostration. All cases, therefore of febrile jaundice of obscure causation, and particularly when there is an association with hæmorrhages, limb-pains, or other symptoms enumerated above, should be fully investigated. It should also be remembered that a non-icteric form of the disease has been described.[2, 10]

In Flanders and elsewhere during the war the epidemics were

curiously localised.[2] This would appear to suggest that rats in some areas are more heavily infected than in others. It would be of interest to discover whether there exists any local variation in the infectivity-rate of rats in this country, and if so what factors might be held to account for such variations. The investigations of Stokes [2] in France and A. C. Coles [5] in this country both supply strong evidence of local variations in the percentage of rats infected. The occurrence of the disease under civil conditions is a further argument for a vigorous anti-rat campaign.

We are indebted to Dr. A. F. Hurst for permission to publish these notes, to Mr. H. B. Butler of Guildford for much valuable help, and to Dr. Pierce, M.O.H. for Guildford, who procured the rats.

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STUDIES ON TUMOUR FORMATION

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V. THE IMPORTANCE OF CONGENITAL MALFORMATIONS IN TUMOUR FORMATION

IT is the fashion to trace the origin of almost every tumour with an unusual or atypical structure to an error of development. A study of the literature almost leads us to suppose that the cells of congenital tissue malformations, and more especially of displacements, regularly end by assuming blastomatous characters. But we have seen, in the preceding studies, that the tissue malformations that are met with in the body are almost invariably characterised by a high degree of differentiation, and by the general absence of a tendency on the part of their cells to excessive proliferation. Undifferentiated "cell-rests" are almost unknown after the earliest months of extra-uterine life, the time at which the tissues have completed their gross development. Whereas tissue malformations are common enough, actual displacement plays a very minor part in their production.

The question, therefore, arises: Since undifferentiated cell-rests are almost unknown in the fully developed body, is it possible that those that do not undergo differentiation develop at once into tumours? In other words: Are all tumours congenital? Common experience answers this question at once: It is not so. This answer alone should be sufficient to discredit Cohnheim's theory.

Again, we may ask: Are the cells of congenital tissue malformations predisposed to tumour formation? Should the answer be in the affirmative, Cohnheim's theory may still be applicable to a large group of cases. The object of this study is to find the answer to this question.

Theories die hard, and an attempt to overthrow one that is as well established and appears to rest on as firm foundations as that of Cohnheim is not to be undertaken lightly. I therefore propose to describe the tumours I have observed, whose cellular structure precludes every hypothesis except the one that they have originated in congenital cell-rests. The frequency, age-incidence, and general behaviour of these may help us to form

definite conclusions as to the nature of the cells in which they have originated. I shall limit myself to tumours that I have examined, so that my conclusions may be based on personal experience. The easiest, and only really satisfactory group to deal with is the epithelial tumours with blastomatous, if not actually malignant, growth. Their structure is generally sufficiently like that of the corresponding epithelia to admit of safe deductions. Again, blastomatous, excessive, independent growth is the only feature that enables us to tell a tumour from a simple malformation with any degree of certainty. It is true that it is a difference of degree only. It is, however, sufficiently obvious in most cases to serve our purpose.

1. *The melanomata.*—I have pointed out in Study III. that pigmented moles or nævi of the skin are extremely common malformations, whose congenital origin there is no reason to doubt. They are distinguished by an excess of pigmentation and by loosening of the cells of the epidermis, which enter the cutis and there form the characteristic groups of nævus-cells. Moles undergo a process of ageing, which depends upon the fact that the nævus-cells have a definite life history, at the end of which they die or, according to another view, which has many points in its favour, are converted into connective tissue cells of the cutis. The production of nævus-cells gradually diminishes and eventually ceases altogether. If we accept the view of the epithelial origin of the nævus-cells, we must include pigmented moles with the choristomata of Albrecht,[1] since they are distinguished by a displacement of epidermal cells into the cutis.

There is a group of blastomatous tumours, the melanomata, which always * arise in pigmented moles. They are by no means common, especially when we remember that the majority of individuals are the possessors of pigmented moles. It is not my object to enter into statistics; not more than two or three a year pass through my hands. Nor are they found in very young subjects as a general rule. Of the sixteen primary melanomata operated on at Guy's Hospital during seven years, one occurred in a girl of 12, one in a girl of 15, one in a boy of 16, and one in a young woman of 20. All the others came from individuals of between 51 and 72 years of age. The average age of these twelve cases is 61¼ years. The gap in the age incidence is remarkable.

The most striking feature of the melanomata is their extraordinary diversity of histological structure. Some are carcinomata, whereas others are equally definite sarcomata. This appears

* I am concerned here only with the melanomata of the epidermis. These tumours are found in the retina and, as pathological curiosities, in certain ento- and meso-dermal internal organs.

to me to be the most interesting of all their characters, and one of no little biological importance. I must reserve its discussion for another occasion. The statement that all melanomata of the skin arise in pigmented moles must suffice for the present.

Melanomata, like other tumours, are usually well established by the time we are able to examine them, and increase in size only by proliferation of their own cells. This strictly autonomous and independent growth is of such general occurrence, that it led Ribbert [12] to make the dogmatic statement that no tumour, once it has definitely become one, ever increases in size by the implication of neighbouring cells, and therefore gives no clue to the changes that have led to its formation. But tumours are occasionally met with, the changes at the edges of which cannot be accounted for in this way, and which present evidence of growth by additions from the neighbouring cells. I cannot otherwise account for the structure of the following melanoma.

The specimen is an ulcerated tumour of the umbilicus of a woman of 20, which had originated in a pigmented mole. Under the microscope it is seen to consist of masses of large round cells, isolated from each other, although their edges are often flattened from mutual pressure. A few delicate strands of connective tissue only are found within these nodules, and subdivide them into indistinct alveoli. The greater part of the tumour is covered by epidermis. It rests on granulation tissue in several places, and appears to have spread over it from the neighbouring skin. Fig. 44 represents one of these areas. Several papillæ are shown. The basal cells of those on the left of the drawing are somewhat heavily pigmented, but otherwise present no anomaly of shape or of position. Towards the right they become heaped locally at the edges of the papillæ. They enlarge and assume the structure of nævus-cells. Nests of these are found among the cells of the stratum granulosum. They become more numerous and larger in the right half of the figure. The large triangular space, covered above by semi-necrotic epidermis, and partly lined by a row of nævus-cells below, some of which can be seen to infiltrate the stroma, represents an epidermal papilla, that has been converted into these cells, and in which liquefaction has taken place. Near the right edge of the drawing there is a nest of nævus-cells within the granulations, and isolated pigmented cells are found among the leucocytes and plasma-cells.

The growth of this neoplasm depends chiefly on the proliferation of the large masses of big nævus-cells that make up the greater part of its bulk. This is proved by the presence of mitoses within them. These cells are parts of a well-established, independently growing, malignant blastoma, and give no answer whatever to the question of its origin. But the appearances

illustrated in Fig. 44 indicate that the formation of fresh young nævus-cells was actively taking place in its epidermal covering at the moment of its removal. No other explanation can account for them. No infiltration with nævus-cells, that have come up to the surface from below to form a secondary union with the epidermis, can explain the orderly and progressive manner in which the changes increase in intensity from left to right in Fig. 44. It is too like the appearances seen in Fig. 21 (III.) for this to be at all likely or indeed possible. Where the cells are largest, most fully developed, and therefore oldest, liquefaction of the stratum granulosum has taken place. Where they are smaller, and where they eventually become indistinguishable from the

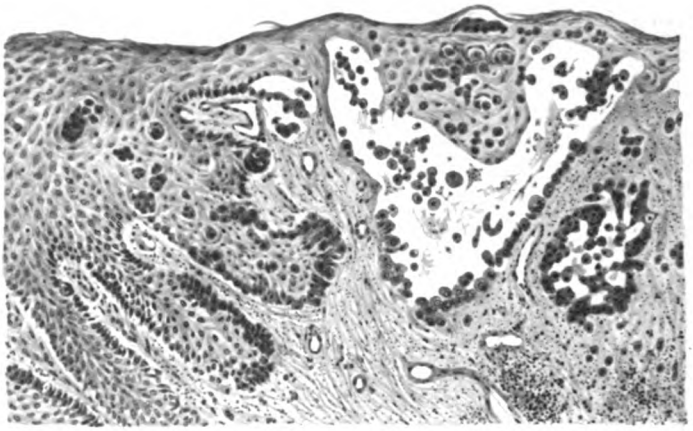

FIG. 44.

Cells of melanoma formed from pigmented mole of umbilicus. Magnif. 95.

heavily pigmented cells of the germinal layer of the epidermis, liquefaction is absent. We have seen in Study III. that a mole is a pigmentary degeneration associated with liquefaction. It is only when we remember the lesson I have tried to expound in the first of these studies, and realise the close correspondence of tumours (even when they are as malignant as this specimen) with malformations and normal tissues, that we are able to appreciate the fact that the part of the melanoma depicted in Fig. 44 is a pigmented mole.

Other parts of the sections show the invasion of the connective tissue by the young, newly-formed nævus-cells in many places. They are given off from the epidermis as isolated cells or in groups. They increase in size, become less densely pigmented, and their nuclei undergo mitotic division. They are now the essential cells of a blastoma.

I can only reiterate that here we have an instance of a large malignant tumour, whose tissues are actually reinforced by young cells given off from an epidermis, which otherwise presents none of the features of blastomatous growth. We are dealing, therefore, with a blastomatous malignant pigmented mole, or, in other words, with a malignant malformation.

It may not be out of place to say a few words here about another kind of " transition," that is frequently described between the cells of carcinomata and those of the surrounding epithelium. It occurs freely in several parts of the specimen under discussion, and is the result of a secondary union of these cells. Here, as well as in the majority of carcinomata of the skin, the elements of the neoplasm have extended to the level of the epidermis, and have proliferated on its deep surface and between its cells, so that they have become inextricably mixed together, and it requires some little patience, as well as knowledge of the condition, to arrive at the correct interpretation. That these appearances are deceptive, and not to be interpreted in the sense of a genuine transformation of epithelium into carcinoma, has been most strongly insisted upon by Ribbert,[12] and demonstrated by Borrmann.[3] These authors maintain that such a transformation never takes place at the periphery of an established malignant tumour. In this they err. I have seen a few instances of it, of which our melanoma is one. These exceptions to Ribbert's doctrine are far too rare to be treated lightly. I have therefore discussed this case at some length. They are of such rarity, that the brief statements often made, that transitions were found at the edges of tumours, should be regarded as errors of observation. They should always be substantiated by a detailed description or, better still, by a good illustration. They refer, in ninety-nine cases out of a hundred, to secondary unions of cells. I have read before now of a tumour whose origin was attributed to a cell-rest, but which nevertheless was said to show true intermediate stages at its periphery. This is extremely bad thinking indeed. For if true transitions are found in an established tumour, it cannot have arisen in an isolated embryonic cell-rest. Conversely, if its origin from such an isolated rest can be proved, intermediate stages between the cells of the neoplasm and those of the neighbouring epithelium, that never have formed a part of the rest, are impossible. They are so unless a cancer toxin is admitted that is manufactured by the cells of the tumour and " infects " other tissues in the true sense of the word. This opinion has long ago been given up by every pathologist. Men like Ribbert and Borrmann were much too logical to admit the possibility of genuine intermediate stages,

since they realised that Cohnheim's theory would receive its *coup de grâce* by such an admission.*

If the statement be true that all melanomata of the epidermis arise in pigmented moles, the deduction is legitimate that their mode of formation is, in the early stages at all events, similar to that described. Since the majority of melanomata, when we are able to examine them, no longer increase in size by additions to their components, but only by multiplication of their own cells, these appearances are but rarely seen.

We cannot determine if the newly-formed nævus-cells are blastomatous from the very first, or whether they acquire malignant properties later. We can, however, state definitely that they arise by a pigmentary degeneration of epithelial cells that exhibit no morphological evidence whatever of blastomatous, or even of hyperplastic growth. The cells of the neoplasm arise in a congenital malformation, it is true, but their formation is in full swing twenty years after birth.

Melanomata are luckily uncommon, whereas pigmented moles abound. I believe that I under-estimate the frequency of the latter when I assume that 90 per cent. of all human beings are their possessors.† We need but compare the relative rarity of melanomata with the frequency of carcinomata of the breast or of many other organs, to reach the following conclusion: melanomata are much less frequent than certain other tumours, whose origin in congenital malformations cannot be demonstrated, granted that 10 per cent., or even 50 per cent. of our fellows are free from moles. The cells of these, the commonest of all congenital tissue malformations, are therefore most emphatically not predisposed to tumour formation to a degree in excess of the other tissues of the body.

In conclusion: the only difference that I can see between a pigmented mole and a melanoma is this. The cells of the former undergo a physiological process of ageing, if the word physiological can be applied to a congenital malformation. Those of the latter fail to do so. They proliferate indefinitely instead. Moles are simple malformations, melanomata are malignant malformations.

It must be remembered, however, that melanomata occasionally grow slowly, and are innocent clinically. This was pointed out by Whitfield [20] more than twenty years ago.

* One of my principal reasons for having nothing to do with endotheliomata is the constancy with which transitions are said to occur at their periphery, even by staunch upholders of Cohnheim's theory.

† Since they are often multiple, the statement that their number is larger than that of individuals is probably nearer the truth.

Since I regard the displacement of epidermal cells as the distinguishing feature of the melanomata, I would emphasise this fact by calling them choristo-blastomata in accordance with Albrecht's nomenclature. The non-committal name to apply to them is that of harmato-blastoma, which indicates merely that they have arisen in connection with a malformation.

2. *Adenomata of præ-parotid lymph-glands.*—We have seen that salivary tubules are frequently enclosed within lymphoid tissue during development. When a capsule is formed around the lymph-gland, these tubules are separated from their normal

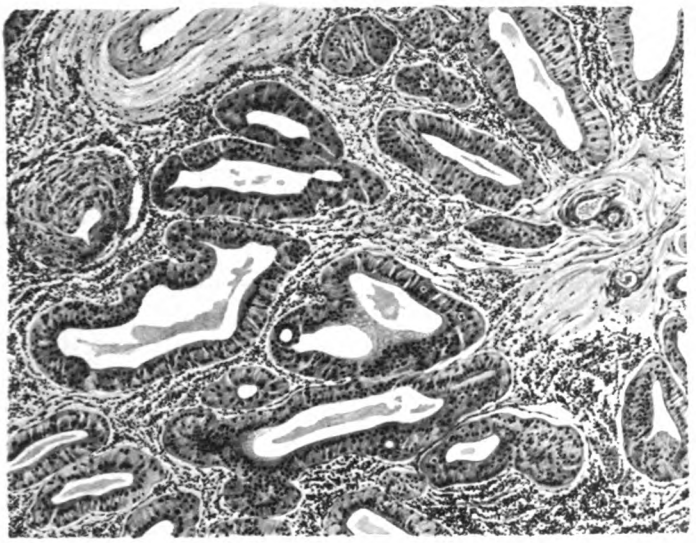

FIG. 45.

Adenoma of præ-parotid lymph-gland. Magnif. 85.

connections, and can persist in an unaltered or more or less atrophic condition within its substance. Fig. 31 (III.) shows them in a præ-parotid lymph-gland of a woman of 25. The anomaly is one of blending in these cases; there is no active displacement of epithelium.

The two following cases * demonstrate that these epithelial inclusions occasionally give rise to tumour formation.

Case 1.—The specimen is a lymph-gland, about 2 cm. in length, dark red in colour, and with numerous small yellow areas,

* I am indebted for both these cases to the Director of Laboratories of the Clinical Research Association, and must thank Dr. Raby for the clinical data of the first, and Sir R. Luce for those of the second, and for permission to publish them.

resembling caseous tubercles, scattered throughout its substance. It had been noticed for a year or two in a man of 50, and had increased somewhat rapidly in size of late. It was situated just below the right angle of the lower jaw, beneath the deep fascia, to which it was slightly adherent.

Case 2.—This gland was removed from a woman of 60. It had been noticed for a few months, and was situated immediately below the right parotid. Its appearance was that of an enlarged, but not inflamed, lymph-gland.

The histological structure of these specimens is identical in its essentials, although it differs slightly in detail. In the first (Fig. 45) the lymph-gland is occupied throughout by large,

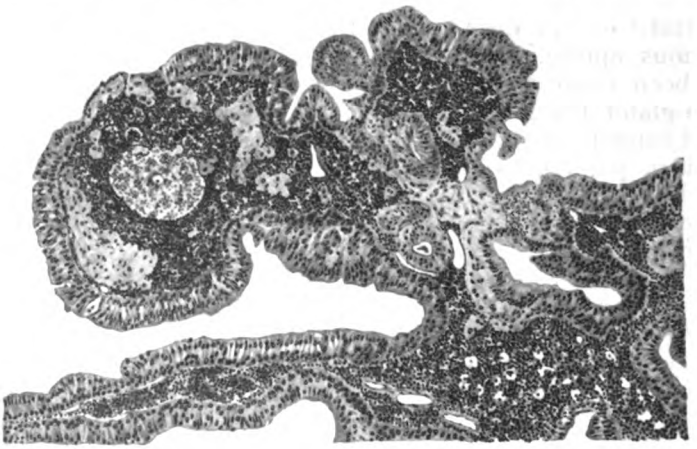

FIG. 46.

Cystic adenoma of præ-parotid lymph-gland, with early infiltration of stroma by epithelium. Magnif. 85.

wide epithelial tubules, whose lining is quite characteristic. It consists of two layers, a basal layer which is somewhat irregular and whose epithelial cells are rounded, and a superficial layer of tall columnar cells, with their nuclei near their free ends. The lumina are occupied by a homogeneous coagulum. The tubules are either in direct apposition with the lymphoid tissue of the gland, or separated from it by a thin layer of areolar tissue. They occupy the position of the lymph-sinuses. The lymphoid parenchyma shows few or no signs of compression. It contains typical follicles with germinal centres. The gland is surrounded by a thin, tough, fibrous capsule. There is no evidence of invasion of it by the cells of the epithelium, nor do they infiltrate the lymphoid tissue.

The second case (Fig. 46) differs from the first in that the

epithelium surrounds large cystic spaces, occupied by granular secretion, into which it projects as irregular branched papillæ. There is also a distinct tendency on the part of the epithelium to invade the lymphoid tissue. The latter is much less abundant than in Case 1, but typical follicles with germinal centres are present. There is no evidence of invasion of the capsule.

The first specimen is an adenoma, the second a cystic-papillary adenoma with, probably, a slight degree of malignancy. They have both originated in lymph-glands. No other tumour with a similar structure was found in either patient,* nor do such tumours occur to my knowledge.

These cases are identical with the two described by Albrecht and Arzt,[2] except for the fact that they found small areas of squamous epithelium in them. Their drawings might easily have been made from our specimens. Their first case was a lymph-gland from the parotid region of a man of 64; their second came from the submaxillary region of a girl of 12. They call them papillary cyst-adenomata, and point out that their epithelium closely resembles that of the ducts of the salivary glands. They derive their tumours from entodermal epithelium, or from a mixed ento-mesodermal cell-rest which has given rise to the lymphoid tissue as well. They believe that the tumour is closely related to salivary epithelium, since they found small ducts in the capsule. They do not, however, draw the conclusion that it is actually of this nature, since they appear to have been unaware of the occurrence of salivary tubules in lymph-glands.

I agree with Albrecht and Arzt that the epithelium of these cases is exactly like that of the ducts of the salivary glands, when they have undergone hyperplastic proliferation in inflammatory conditions. Since inclusions of parotid and submaxillary tubules are known to occur within lymph-glands (Fig. 31 [III.]), I have no hesitation in claiming that these cases are instances of tumour formation of heterotopic salivary epithelium. They are hamarto-blastomata, since they owe their origin to a malformation, or anomaly of blending.

It is impossible to decide, from a study of these tumours, whether they have originated in undifferentiated epithelium or true "cell-rests," or in tubules that had reached the stage of differentiation of those in Fig. 31 (III.). It is quite useless to pursue this line of thought for the present, since these tumours are fully established, and every clue to the state of differentiation of the cells from which they have grown has been lost long ago. Since we have no evidence to go on, we should only follow

* Case 2 had a carcinoma mammæ, whose structure was entirely different.

the example of the numerous writers who attempt to show, with varying degrees of assurance, that an established tumour has arisen in a dormant cell-rest, roused to activity and endowed with life itself for the occasion. We should but indulge in vain and unprofitable speculations.

There is, however, one conclusion to be safely drawn from a comparison of the structures illustrated in Fig. 31 (III.) with those in Figs. 45 and 46. It is this: epithelial cells, after they have been separated from their normal surroundings and enclosed within other tissues, persist in some cases in a differentiated condition, whereas in others they give rise to and are replaced by a tumour, even after the lapse of a great number of years. But in this respect they do not differ from the other tissues of the body, in which, as I have said before, no congenital anomaly can be demonstrated.

There is no evidence even that these malformations are "predisposed" to tumour formation to a higher degree than the other tissues. They are apparently common enough in the fœtus (*vide* Study III.), but we have absolutely no data concerning them in later years. Until tissue malformations are systematically looked for and carefully studied, our conclusions will no doubt require frequent revision. Such an investigation on a large scale can only be carried out in a big pathological institute.

Albrecht and Arzt's [2] second case occurred in a girl of 12. The other three concern individuals of between 50 and 64. This age incidence is strikingly like that of the melanomata I have observed.

3. *Papillary cystic adenoma of accessory thyroid.*—Unfortunately, all that I know of the specimen illustrated in Fig. 47 is that it was a cyst of the neck, which was not connected with the thyroid. The histological preparations possess the structure of a cystic adenoma of the thryoid, with a good deal of proliferation of epithelium, and the formation of irregular branched papillæ with a hyaline stroma. The papillæ project into spaces occupied by a granular albuminous coagulum, which has been omitted from the drawing. A characteristic feature of the specimen is the presence of islands of non-keratinised squamous epithelium, the largest of which is represented in Fig. 47.* They are solid, and possess no connective tissue stroma. The cells of the rete Malpighii are situated at their periphery, those of the centre are compressed and laminated. The cross sections of these islands have a singularly isolated appearance. They

* In my endeavours to draw this island accurately, I find I have unintentionally exaggerated the size of the nuclei slightly.

arise from solid masses of epithelium, among the columnar cells that line the papillæ.

It is reasonable to assume that this papillary adenoma originated in a persistent remnant of the thyro-glossal duct. We have seen that these remnants are not uncommon, and that they sometimes undergo differentiation into thyroid tissue (Fig. 19 [II.]). Adenoma formation is very common in enlarged thyroids; in the case under discussion it has taken place in an unobliterated part of the duct. No deductions can be drawn concerning the state of the epithelium in which this adenoma has arisen. Figs. 19, 20, and 47 suggest that they represent three stages of the same process. It is quite as impossible to

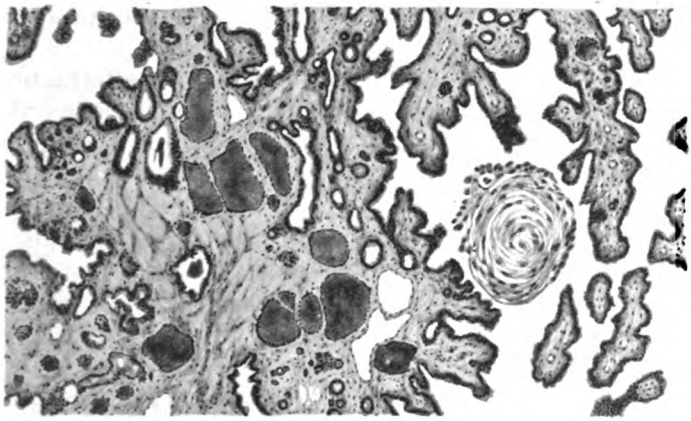

FIG. 47.

Papillary cystic adenoma of accessory thyroid. Magnif. 85.

show that our adenoma must have arisen in an undifferentiated cell-rest, as it is to prove a similar origin for an ordinary adenoma of the thyroid. Here, again, the finished neoplasm throws no light on the manner of its formation.

The presence of squamous epithelium in this tumour is an instance of heteroplasia.[10] It shows that the epithelium of the thyro-glossal duct can undergo differentiation in the direction of that of the buccal mucous membrane as well as into more highly organised thyroid epithelium. Squamous epithelium has been found in the thyroid gland and in its new growths, so that this potentiality is shared by all parts of the duct. It is no evidence that the cells of those parts of it which normally disappear during development have remained, should they persist, in a condition approaching the " embryonic."

Since this tumour has originated in a persistent part of the

thyro-glossal duct, it is a hamarto-blastoma of Albrecht. It has been formed *in situ* without displacement.

4. *Carcinoma of accessory pancreas.*—As I did not include accessory pancreatic tissue among the malformations described in Study II., it becomes necessary to say a few words about it here. This tissue is situated either between the layers of the mesentery, or within the wall of the stomach or small intestine. The latter variety need only be considered here. It is usually submucous, reaching to and often within the *muscularis mucosæ* on the one side, whereas, on the other, it penetrates the muscular coats for a variable distance. The glandular acini, whose structure is typically that of the pancreas, communicate with the lumen of the gut by means of one or more ducts. Frequently, however,

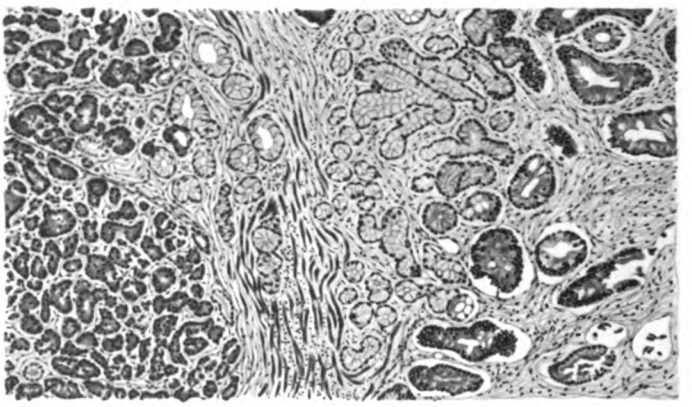

FIG. 48.

Accessory pancreas on pyloric end of stomach. Magnif. 85.

the deep ends of the crypts of Lieberkuehn, or of Brunner's glands, are lined by pancreatic epithelium, which is directly continuous with the acini of the accessory organ. Or, the intestinal glands are prolonged into the submucous tissue, where they end blindly or are connected with the accessory pancreas. Again, Schridde [16] has shown that the part of the mucous membrane of the stomach that covers the specimens found in this viscus sometimes has the structure of that of the duodenum. His view that these submucous pieces of pancreatic tissue are heteroplasias, produced by an abnormal differentiation of the epithelium of the intestine, thus appears to be the correct one.

Fig. 48 represents a submucous accessory pancreas of the stomach, one inch above the pylorus. Brunner's glands, which, however, occur normally at this level, are seen beneath the *muscularis mucosæ*. Two of them are continuous with pancreatic

tissue after the manner described above. (I reproduce this drawing here to facilitate a comparison of the structure of an accessory pancreas with that of the tumour now to be described.)

At the post-mortem examination of a man of 57, who had died from head injuries sustained in an accident, a firm oval tumour was found on the greater curvature of the stomach a short distance above its middle. It measured 4 cm. in its greatest diameter, and occupied the entire thickness of the wall of the organ. It was thought to be a fibro-myoma of unusual size. No other new growth was found, and the pancreas was without anomaly.

Histological examination shows that the specimen is a carcinoma (Fig. 49). It is surrounded by a capsule, which is

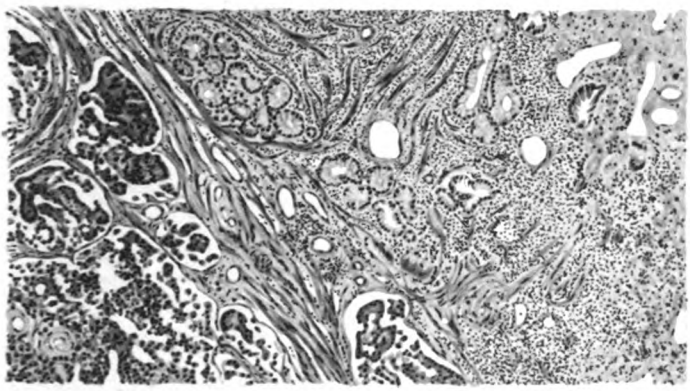

FIG. 49.

Carcinoma of accessory pancreas on stomach. Magnif. 85.

infiltrated by its cells. They extend beyond its limits into the mucous membrane of the stomach, and beneath its peritoneal covering. The tumour is almost entirely necrotic. Only at its periphery is there a narrow growing edge of tissue, whose characteristic structure has been retained. On comparing it with Fig. 48, with normal pancreas, and with carcinomata of this organ, there can be no question that it is composed entirely of carcinomatous pancreatic epithelium. Since there was no new growth of the pancreas, the only possibility that remains is a malignant accessory pancreas. The mucous membrane of the stomach covering it is inflamed and extensively disorganised. A few oxyntic cells, however, remain.

I have found only two cases of carcinoma of an accessory pancreas in the literature. Seidelin [17] describes a small carcinoma of the jejunum, whose periphery has the structure of

atypical pancreatic tissue, and has invaded and destroyed the intestinal mucous membrane. Herxheimer [5] (p. 245) mentions an extensive carcinoma of the small intestine, which he believes to have arisen in an accessory pancreas.

The only conclusion that can be drawn from this specimen is that it is a carcinomatous accessory pancreas on the stomach. No inferences are possible concerning the manner of its formation, or the time at which malignancy supervened. Although there are many recorded instances of accessory pancreas, the rarity of carcinoma of this anomaly does not suggest a predisposition of its cells to blastomatous growth. Again, the comparatively advanced age of our subject is of interest.

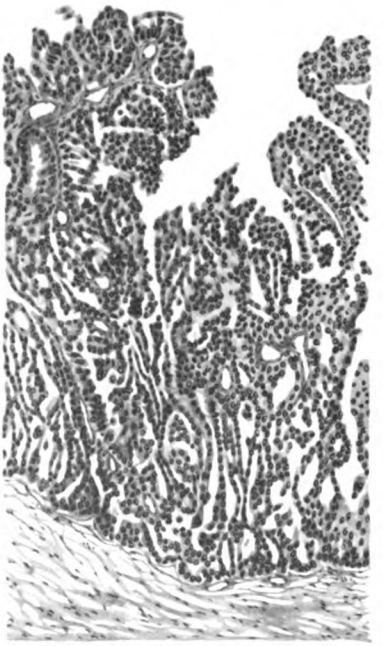

FIG. 50.

Cystic papillary adenoma of broad ligament. Magnif. 85.

Since accessory pancreatic tissue is an instance of heteroplasia or abnormal differentiation of the epithelium of the gut, our carcinoma is a hamartoblastoma of Albrecht. There is no evidence that displacement has played a part in its production.

5. *Cystic papillary adenoma of broad ligament.*—The specimen is a large broad ligament cyst that was removed from a woman of 58; its clinical history and naked-eye appearance present no peculiarities, except that it is lined by an unusually thick velvety and slightly villous mucous membrane. It contained the usual limpid, faintly blood-stained fluid. Fig. 50 represents a part of its lining, which is uniform throughout. It consists of scattered, extremely delicate, branched connective tissue papillæ, with thin-walled blood vessels, separated by groups and irregular columns of cubical and cylindrical epithelium, that is arranged around irregular lumina. It rests on a delicate fibrous stroma, that is condensed under it to form a kind of basement membrane. There are no signs of infiltration of the stroma by the epithelial cells. The specimen is clearly a papillary adenoma.

Since the cyst was found between the layers of the broad ligament, it is obviously an instance of a "broad ligament cyst," whose origin from remains of the Wolffian body or duct is universally admitted. Whereas these cysts are usually lined by one or two layers of cubical cells, at most thrown into folds by connective tissue papillæ, the present instance is distinguished by blastomatous growth of the epithelium.

The parovarium, or the rudiment of the Wolffian body in the female, is, as I have pointed out, a normal organ with a great variation in size in different individuals. Since it attains its highest degree of development in the embryo, its remains in the adult are to be looked upon as borderland cases between normal and abnormal persistence of tissue, and can therefore be included

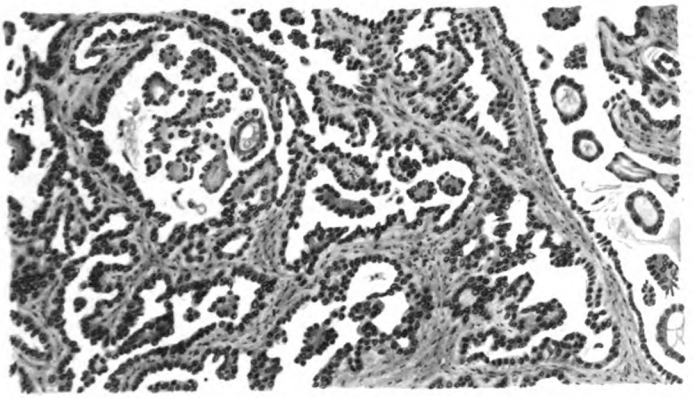

FIG. 51.

Papillary carcinoma of vagina. Magnif. 90.

among the hamartomata. Our papillary adenoma is thus to be regarded as a hamarto-blastoma of Albrecht. Since it formed a complete lining to the cyst, it is impossible to draw conclusions concerning the nature of the cells in which it originated. The fact that the patient was 58 years of age, and that there is no evidence of malignancy, are of interest.

6. *Papillary carcinoma of vagina.*—The tissue illustrated in Fig. 51 was removed for histological examination from the vagina of a woman of 64. She died a few days later. Only a local examination was allowed. The vault of the vagina was occupied by an ulcerated new growth, which extended around the whole of its circumference to about its middle. The tumour had invaded the cervix uteri, whose remains were present in its upper part. The external os was recognisable, and the cervical canal was patent, although its walls were covered by growth.

This extended to the level of the internal os, the body of the uterus being free from it. There was extensive infiltration of the base of the broad ligaments, especially on the left side.

It is most unfortunate that the disease was too far advanced to have revealed on examination the part of the vagina in which it originated. All that can be said is that the vault of this organ was chiefly affected, especially on its left side, and that the cervix uteri appears to have been invaded by the new growth. The histology of the specimen, however, settles the question of its origin. Fig. 51 shows it to be built up of irregular branched tubules, that are often dilated into cysts of varying size, into which numerous papillæ project. Meyer [8] was the first to describe a carcinoma of the ampulla of Gaertner's duct in the vault of the vagina, whose structure corresponds exactly with our case. Again, it is clearly built up on the same plan as the broad ligament cyst in Fig. 50. I therefore feel no hesitation in claiming that this papillary carcinoma has arisen in the ampulla of Gaertner's duct.

I therefore include the case with the hamarto-blastomata. It differs from the adenoma of a broad ligament cyst described above in its degree of malignancy, but agrees with it in the late period of life at which it first gave rise to symptoms.

I have seen two papillary carcinomata and one tubular carcinoma of the cervix, whose structure precludes this diagnosis. That of one of the papillary tumours is too indefinite to allow conclusions; the other two have certainly arisen in the epithelium of the cervical canal.

7. *Embryonic tumours of the kidneys.*—I have given a general description of these tumours in Study I. (Fig. 8). I tried to emphasise their close resemblance to early stages of development of the kidneys. The truth of this contention is borne out by Fig. 52, where irregular masses of round cells are to be seen, whose nuclei tend to be arranged in the shape of rosettes around small areas of cytoplasm. The latter soon disappears, and is replaced by a space, around which the nuclei assume a definite epithelial arrangement. More or less highly differentiated tubules are formed, with clear-cut, sharply defined lumina. But the round cells undergo differentiation in another direction. They become spindle-shaped and elongated, and give rise to the mesenchyme of the tumour. This contains many long, rod-shaped nuclei, which belong to fully differentiated plain muscle cells. It is probable that the majority of the elements of the mesenchyme are of this nature.

These embryonic tumours of the kidneys appear to me to

afford the clearest evidence that some of their cells are at a very primitive level of differentiation. I refer to the round cells which give rise to epithelial tubules on one side, and on the other to the mesenchyme of the tumour. They are its only elements that, in addition to undergoing differentiation in these two directions, divide and multiply indefinitely in their original form, and are responsible for the increase in size, and for the malignant properties of the tumour. When their descendants differentiate into epithelium or mesenchyme, their power to proliferate becomes less. It diminishes coincidently with the degree of differentiation attained, until in the most fully developed tubules and muscle cells it corresponds with that obtaining in these tissues in the body generally.

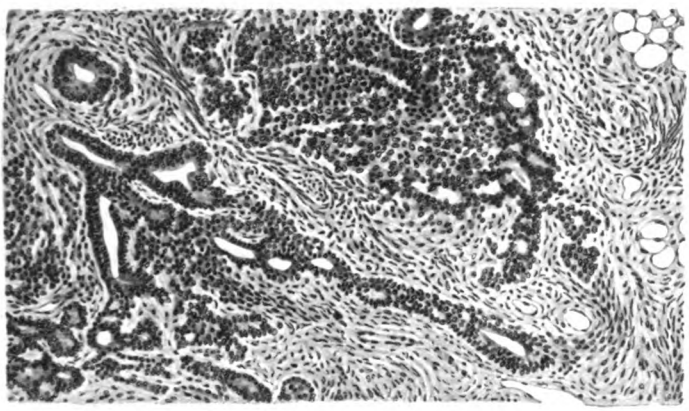

FIG. 52.

Embryonic tumour of kidney. Differentiation of round cells into epithelial tubules and mesenchyme. Magnif. 115.

Since these round cells divide and undergo a partial differentiation, they appear to possess all the prospective potentialities of those of the renal blastema in the embryo. This being so, they are of the same nature; they are primitive mesoblast cells, or embryonic cells in the strictest sense of the word. I am forced to disagree with MacCallum [6] (p. 1030), who regards the cells of tumours in the light of cells that are modified to such an extent, that their sole function is to reproduce themselves rapidly, for which reason they never assume the forms of normal cells. He maintains that tumour cells do not pass through a regular development to become mature, but that they merely continue to grow and divide. To my mind, the essential characteristic of the cells of tumours in general,* and of those of embryonic

* *Vide* the first of these studies.

tumours of the kidneys in particular, is the constant endeavour to undergo the same orderly steps in differentiation that are taken by those of the corresponding tissues of the body. Many of them succeed to a high degree, and very good imitations of renal tubules and of plain muscle, which is abundant in the earlier stages of development of the kidneys, and which, as Dr. Harvey assures me, is almost equally so in these organs in adults, are reproduced. I agree with Trappe,[18] who considers these tumours to be neither more nor less than embryonic kidneys. They only differ from these in one essential, in that they are unable to undergo full differentiation. The desire, so to speak, is there to undergo it, but it is never fully consummated.

What is the reason of this difference? Trappe has pointed out that it must depend either upon an inherent defect in the power of self-differentiation, or upon the action of external stimuli. He leaves the question open. I believe that the second explanation is the true one. In the specimen from which Fig. 8 (I.) has been drawn, many solid glomeruli are present, one of which appears in the drawing. They never contain capillaries. As I have attempted to show,[10] the stimulus to full differentiation of the glomerular epithelium into flat cells is therefore absent. The only possible alternative for its cells to take, since they are prevented from becoming fully differentiated, is to proliferate indefinitely. I believe that these glomeruli, or pro-glomeruli, as I have named them, would eventually have developed into mature structures, had they formed normal connections with the vascular system. As these connections were absent, differentiation was impossible, and the only alternative that remained was unlimited "malignant" growth. This observation appears to me to touch very closely on some of the fundamental questions of tumour formation. It suggests that the cells of tumours are essentially normal cells, that were originally identical with those that later take part in the formation of normal tissues, and subserve useful functions. That they have gone astray is not their own fault so much as that of their environment.* This has been and has remained such that orderly differentiation became impossible. The

* Two days after writing this I received from Mr. Morley Roberts a copy of his most suggestive paper on Malignancy.[14] He makes use of the following words: "The prodigious fertility of embryomas in such products suggests that the imperfect parent tissue is doing its best to be normal, if the phrase is permissible; but that such a result is impossible owing to the necessary lack of normal excitation and inhibition, *i. e.* of the usual environment" (p. 53). That his philosophical mind should have formed the same conclusions from wide biological and physiological data, to which I have been drawn by histological material, justifies the claims of morbid anatomy no longer to be regarded merely as the "study of dead meats," and to be allowed a place among the living sciences.

present instance is a concrete and exceedingly apt one of the class of phenomena that Ribbert [12] referred to under the name of " defective tissue correlations."

Questions such as this will have to be more fully considered at the end of this series of papers. To return to the subject matter of this study, embryonic tumours are almost exclusively found in infants and young children, and have even been observed in the fœtus, *e. g.* by Weigert.[19] A few cases have occurred in adults. Muus [9] found one in a woman of 34. Embryonic tumours of the kidneys are observed with about the same degree of frequency as the melanomata. They are not common, although they are by far the commonest new growths of these organs found in young children.

I have said just now that these tumours are malignant malformations. The kidneys are the seat of corresponding simple anomalies. These are common enough when slight, whereas advanced cases are only about as frequent as embryonic tumours. I refer to congenital cystic kidneys. They are built up of dilated glomeruli and secreting tubules, that always end blindly at some point above where they should communicate with a collecting tubule. Cases that can be studied in very young children demonstrate that the cysts occur in groups, between which there remain more or less extensive areas of functionating kidney substance. The very slightest cases of all are represented by the cysts described in Study II., and illustrated in Fig. 12. As age advances they enlarge, because of the accumulation of secretion within them, and give rise to the multiple or isolated cysts so frequently seen in the kidneys of adults. Proliferation of the epithelium of the cysts generally takes place in advanced cases, and may in rare instances lead to the production of papillomata and even of carcinomata. These changes are secondary; they are later stages of the epithelial proliferations described in a cystic horse-shoe kidney in Study I. (Fig. 10).

Embryologists were long divided as to the developmental history of the kidneys. Two views were entertained. According to the older, or monistic view, the whole of the kidney is developed from outgrowths of the upper end of the ureteric diverticulum of the Wolffian duct. According to the more recent, or dualistic view, this structure gives rise only to the collecting tubules. The glomeruli and secreting tubules are derivatives of the intermediate cell mass, and have to form connections with them. When these fail, the blind secreting tubules are distended by accumulated urine, and cysts result. The dualistic view is now generally accepted. It alone explains

cystic kidneys in a satisfactory manner. I even go so far as to say that these malformations prove its correctness conclusively, and that, had embryologists possessed any knowledge of morbid anatomy, it would have been universally accepted long ago.

I would here draw attention to a paper by Schmey,[15] who discusses analogous malformations in the kidneys of horses. These anomalies demonstrate the fact that the glomeruli, loops of Henle, and convoluted tubules arise in the intermediate cell mass, whereas the collecting tubules must be derivatives of the Wolffian duct.

Cystic kidneys are clearly a result of imperfect and faulty blending of tissues; of a defective tissue correlation. If we compare them, pigmented moles, epithelial tubules within lymph-glands, accessory thyroids and pancreas, and the remains of the Wolffian body and duct in the female on the one side with embryonic tumours of the kidneys, melanomata, and the blastomata of the accessory and vestigial organs described above on the other, we see that the members of the second group represent blastomatous proliferations of the whole or of a part of the corresponding simple tissue malformations. If now we examine the second group, we find that no deductions can be drawn in respect of the histiogenesis of the adenomata of lymph-glands, and the tumours of the accessory thryoid, pancreas, and of the remains of Gaertner's duct, since they are all much too far advanced. We can only say of them *that* they have arisen in these structures, but not *how* they have done so.

The case is different with the melanoma described at the beginning of this paper. There is direct evidence that its essential cells, although they form part of a malformation, are not themselves congenital, in any sense of the word, since their production was in full swing at the time of extirpation of the tumour. If all melanomata arise in very much the same manner, a view for which there is plenty of evidence, they differ from pigmented moles only in the increased amount and rate of the passage of epithelial cells into the cutis. This corresponds with the accelerated growth of the mole as a whole; with the moment at which it has become malignant. This moment is accurately known in a good many cases, since it frequently coincides with the application of an irritant to the mole, in the hope of removing it. I cannot see, therefore, that melanomata prove anything beyond the fact that malignant blastomatous proliferation can and does take place in the tissues of congenital malformations. As was to be expected, they are not immune to tumour formation. Melanomata certainly fail to prove that

congenital malformations are more liable to blastomatous growth than tissues in which no anomaly can be shown to have existed, since they are uncommon tumours, whereas moles are almost universal. Their histiogenesis, in so far as we can study it, their clinical history and frequent onset in response to an irritant, their age incidence, and above all, their comparative rarity, are far removed from forming evidence in favour of the hypothesis that the majority or all (Ribbert [13]) tumours arise in congenital malformations or cell-rests. They suggest that this hypothesis has been advanced and accepted on very inadequate grounds.

Embryonic tumours of the kidneys differ from melanomata in two important particulars. They are about as frequent as cystic kidneys, that represent the corresponding simple malformation, and are found almost exclusively in young children. But cystic kidneys do not represent the malformation in its original form. It has been extensively altered by accumulation of secretion, which in its turn has produced a reactive proliferation and fibrosis of the surrounding connective tissue. These malformations perform physiological functions. Urine is secreted by them, but accumulates on account of the absence of natural communications with the efferent ducts. The presence of definite functions in cystic kidneys, and their absence in embryonic tumours, can only depend upon their respective states of differentiation. In the former it approximates to the physiological, in the latter it does not exceed the degree attained in the earlier months of embryonic life. And even this slight amount of differentiation is not reached by all the cells of the tumour. Many of them remain entirely undifferentiated. Since for some reason or other, they cannot undergo differentiation, the whole of their energy is spent in the only possible alternative direction, that of growth and proliferation.

Cystic kidneys and embryonic tumours represent different end results of the same original malformation. This is but rarely seen in its unaltered form. Meyer's [7] case, which approximates to it, has already been reported at length in Study II. I have recently had the good fortune to see a somewhat similar case in a full-term anencephalic fœtus.

The kidneys appear to be perfectly normal to the naked eye. They are of the usual size and consistency. Cortex and medulla are distinct from each other, the pyramids and calyces, pelves and ureters are quite typical. On histological examination, however, the remarkable appearances illustrated in Fig. 58 are seen. Very few glomeruli and secreting tubules are present. The former correspond in their development to the age of the fœtus. They all contain capillary tufts. This is very evident

in several intensely engorged areas. A few glomeruli are cystic, or atrophied and hyaline. Many of Henle's loops are channelled and possess distinct lumina. The convoluted tubules are invariably solid, without a trace of lumen formation. In many of them the nuclei have disappeared, and the epithelium is swollen and necrotic. The medullary rays are well marked, and contain much plain muscle. The collecting tubules are mostly solid. Lumina are, however, apparent in some of the biggest of them. The subcapsular neogenic zone, which is a constant feature of the kidneys during the later months of development, and in which new formation of renal tubules takes place until at least a year after birth, is entirely wanting. The general stroma is loose and acellular, and accounts for the size of the kidneys. Many thick-walled arteries and wide thin-walled veins are present.

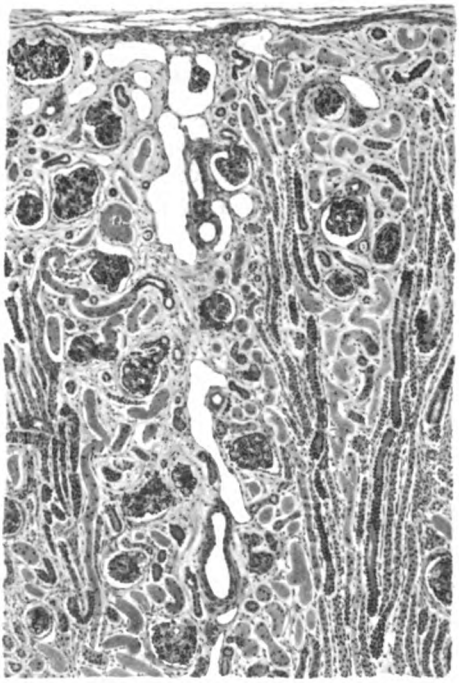

FIG. 53.

Arrest of development of kidneys in anencephalic fœtus of ninth month. Magnif. 85.

The protophase* of the kidneys must, in this case, either have been primarily hypoplastic and defective, or else have undergone a precocious differentiation at a time when normally its cells only differentiate in part, and are still in a state of active proliferation. I do not know which of these explanations is the true one. I prefer the second, since it suggests the action of an abnormal environment, possibly dependent in some way on the malformation of the central nervous system, and relieves us of the necessity of postulating a *vitium primæ formationis*, a sure way of closing the discussion. All that can be said with certainty about this anomaly is that it has not been caused by a defect of the upper end of the Wolffian ureteric diverticulum, or by failure of union

* I am indebted to Mr. Morley Roberts for this word. It expresses all that is suggested by the word "anlage," and does not suffer from the disadvantages of "primordium."

of the two parts of the kidney. Differentiation, although precocious in the time of its onset, was delayed. The delay chiefly involved the convoluted tubules, just as in Meyer's [7] case, and in spite of the different histiogenesis of the latter. There are no signs of excessive proliferation of the constituents of the kidney. The changes are all in the opposite direction, since there is extensive degeneration and necrosis of the convoluted tubules. Here, then, we have a hypoplasia or arrest of development of the whole kidneys, followed by a by no means unsuccessful attempt at normal differentiation.

Instances like this represent a stage nearer to the original malformation than we see in cystic kidneys. Yet differentiation is far advanced, and has obscured and altered the picture. In order to see the tissue malformation that forms the basis of embryonic tumours in its unaltered state, we must turn to cases like those of Fischer.[4] * He described small areas of undifferentiated renal blastema in the kidneys of cases of tuberous sclerosis of the brain. I have discussed his observations in a footnote to Study II. These areas correspond in every respect with early stages of development of these organs. But they correspond equally closely with the structure of embryonic tumours. If either of the epithelial nodules in Fig. 52 were to be found by itself among the tubules of a normal adult kidney, it would be described without hesitation as an island of undifferentiated blastema, or a " cell-rest." I conclude, therefore, that embryonic tumours are simply enormous " malignant cell-rests." Their structure has undergone no fundamental changes from the moment of their inception. From an early period of embryonic life it has always been the same. It is unnecessary, and I believe it to be wrong, to assume that they were ever innocent or simple hamartomata. They are, and have always been, hamarto-blastomata.

But whereas the other parts of the kidney have undergone physiological development, the protophase of our tumours has remained undifferentiated. Why this should have happened I cannot tell. Nor do I know why in one case the protophase should undergo differentiation into a cystic kidney, whereas in another it should fail to do so. But, then, no one can tell me

* Pohl [11] has shown that the areas of undifferentiated renal blastema in the deep layers of the cortex are nothing more than the turned-in edges of the " neogenic " zone of developing tubules that forms caps to the individual renculi. They are strictly localised to the septa between them. In the long series of kidneys he examined of fœtuses and children to the eighth year of life, he only found these incompletely differentiated areas once after the first year in a child of two. He concludes that they normally attain maturity and therefore cease to exist by the end of the first year.

what causes the cells of a small part of the primitive gut to proliferate until they form the vast bulk of the liver, whereas those of a much larger segment, the vitelline duct, usually disappear without leaving a trace behind them. Until the mechanism of growth will be better understood, it appears presumptuous to me to try to offer a cut-and-dried explanation of abnormal growth, of which tumours are the most extreme examples. I have given my reasons in an earlier part of this paper why I believe in the importance of a certain big and hardly understood class of phenomena, known vaguely as tissue correlations, in normal and pathological growth. Their endless variety and great importance have been fully discussed by Morley Roberts [14] in his chapter on " Malignancy."

Melanomata increase in frequency with age, whereas very few embryonic tumours of the kidneys have been found in adults. It is at least possible that these may have been present since childhood, and that they represent more highly differentiated, and therefore less actively growing varieties of these tumours. Why embryonic tumours are generally highly malignant, and but rarely possess a slow rate of growth is, I believe, sufficiently explained by their histology. The structure of their cells warrants, as we have seen, the conclusion that they represent pieces of the kidney at a very early stage of development. The exact stage varies in different cases; this has been demonstrated by Trappe.[18] It, however, always corresponds with a period at which differentiation is slight, and the rate of growth proportionately high and vigorous. The tumour persists at this early stage of development. Its rate of growth therefore remains unaltered. But the surrounding renal tissues become more and more fully differentiated, and their rate of growth steadily diminishes. A disproportion is established. This steadily increases until, at or soon after birth, it attains its maximum. The cells of the tumour, when compared with those of the kidney, now proliferate at a rate which is many times greater. All the features of malignancy cannot, of course, be explained in this way. It indicates, however, that the degree of malignancy depends primarily on the degree of differentiation. It is a fundamental character of the cells, and not a new biological property that has been acquired by them. Exceptionally highly differentiated embryonic tumours of the kidneys must necessarily grow more slowly, and therefore be comparatively non-malignant, since they represent a relatively late stage of development.

Embryonic tumours are found with about the same degree of frequency as cystic kidneys. Since both these malformations, the blastomatous and the simple one, can only have originated

in arrests of development or cell-rests, it would appear that about 50 per cent. of these are predisposed to tumour formation. This is certainly a very high percentage indeed, and gives strong support to Cohnheim's theory. But it suffers a great fall when we remember that cysts of the kidneys, which are certainly congenital, and late stages of the same malformation, are quite common. Since, however, they are very much less common than pigmented moles, it is but kind to Cohnheim to make the most of them.

I must confess that the discovery (Fischer [4]) that undifferentiated cell-rests have been found in an individual of 16 came as a severe blow to me. But, after all, new and unusual facts should be stimulating, since they indicate that many alternatives are possible during histiogenesis, some of which are perhaps never taken, because the exact conditions that favour their development are never present.* The mere fact that these embryonic cell-rests are always associated with tuberous sclerosis suggests that some quite exceptional influence is at work, of which we know nothing. The influence of the central nervous system on growth and on its anomalies is, I was going to say, perhaps one of the least understood chapters of development, but then our knowledge of the effect of every kind of environment on the developing organism amounts practically to nil. I still believe that my contention applies generally, and that cell-rests do not remain dormant. Unless they are absorbed, they either undergo differentiation, or, as embryonic tumours of the kidneys teach us, they proliferate from the beginning as blastomatous or malignant tumours.

Albrecht,[1] who coined the term, believed that choristomata are peculiarly predisposed to tumour formation. The only tumours I have seen that I feel justified in placing among the choristo-blastomata are the melanomata. Albrecht greatly overrated the importance of displacement in the production of malformations. Hence the discrepancy between our views. I have shown in Study III. that accessory suprarenals are choristo-

* Since an argument of this kind may appear to be quite beside the point, I am impelled to quote some passages of Driesch (*The Science and Philosophy of the Organism*, Vol. I, London, 1908) in its defence. In his analysis of the limitations of natural selection, we read (page 264): "Systematics, of course, has to deal with the totality of the possible, not only of the actual diversities; it, therefore, must remember that more forms may be possible than are actual, the word 'possible' having reference, in this connection, to originating, not to surviving. Moreover, systematics is concerned not only with what has been eliminated by selection, but also with all that might have originated from the eliminated types."[1] Again (p. 258): "There may be many substances theoretically known to chemical systematics which have never yet been produced, on account of the impossibility of arranging for their proper conditions of appearance, and, nevertheless, they must be said to 'exist.' 'Existence,' as understood in systematics, is independent of special space and of special time."[1]

mata. Yet I have not included the "hypernephromata" in this paper. I hope to show in Study VI. why I have omitted them.

The last point to be considered is the age incidence of these tumours. Melanomata are most common in late life. Twelve of my cases averaged 61¼ years. The other four occurred in the second decade. Of the four cystic adenomata of cervical lymph-glands described by Albrecht and Arzt [2] and by me, one came from a girl of 12, the others from people of 50 or more. The tumours of accessory pancreatic tissue and of the remnants of the Wolffian body and duct in women were found about the sixtieth year. Embryonic tumours of the kidneys, on the other hand, almost invariably give rise to symptoms during the first years of life. Some have been proved to be congenital (Weigert [19]). The oldest recorded case was aged 34 (Muus [9]). This difference in the age incidence of our renal tumours and of the others is sufficient by itself to cast grave doubts on the applicability of Cohnheim's theory. I have attempted to show in this paper that the former are essentially proliferated malignant "cell-rests." If, as is implied by Cohnheim's theory, the environment of undifferentiated cell-rests becomes more and more suitable for their growth as age advances,* then why do the only tumours for which we have good reasons to believe that they actually arise in them, almost invariably prove fatal at a very early age? It is my belief that all the neoplasms considered in this study, with the exception of embryonic tumours of the kidneys, arise in the differentiated cells of congenital malformations in precisely the same manner as others arise in organs and tissues that were normal at some time prior to their inception. We do not know why or how they arise. Cohnheim's theory does not help us to explain them in the least. In fact, it does much harm, since it distracts our minds by offering a spurious explanation, and inhibits us from pursuing other and perhaps more fruitful lines of inquiry.

Conclusions

The cells of epithelial blastomata alone are sufficiently characteristic to allow of a comparison with normal tissues. Hence sound inferences concerning the histiogenesis of tumours can be drawn from them alone.

* Even if this be true, why should it not apply equally to differentiated cells?

Epithelial blastomata, whose structure points to the conclusion that they can only have arisen in congenital malformations, are rare. With the exception of melanomata and embryonic tumours of the kidneys they are so rare as to form pathological curiosities.

Most of them are fully developed and firmly established. We can only deduce from them *that* they have arisen in cell-rests, not *how* they have done so. Their rarity lends no support to Cohnheim's theory that malformed and displaced tissues are predisposed to tumour formation.

Those that remain appear to have originated in one of two ways. The first is exemplified by the melanomata, that arise *de novo* in the differentiated tissues of congenital pigmented moles, often at an advanced age and in response to a change of environment, such as an irritant. Their biological properties lend no support to the view that the cells of congenital malformations are predisposed to blastomatous growth to a higher degree than those of tissues in which no such malformations can be demonstrated. They entirely fail to support Cohnheim's theory.

Embryonic tumours of the kidneys illustrate the second mode of origin. Since they are probably always congenital, they suggest that the cell-rests in which they arise do not remain dormant, but proliferate from the first. They retain their embryonic rate of growth unaltered. Since this is very high when compared with that of the differentiated tissues of the body, blastomatous proliferation is one of the essential biological properties of these tumours. As they are rare in comparison with congenital cysts of the kidneys, they support Cohnheim's theory only to a limited extent.

The truth appears to be that cell-rests usually undergo differentiation together with the other tissues of the body. In rare cases they fail to do so. In the conditions that usually obtain within the body they proliferate. The only certain instances of this that have come under my personal observation are embryonic tumours of the kidneys. The cell-rests proliferate in accordance with the rule that differentiation and growth are antagonistic. In one quite exceptional case they have been known to persist in an undifferentiated state for sixteen years.

Since cell-rests behave in different ways, it is at least possible that they are influenced by external factors—by their environment.*

Tissue malformations or differentiated cell-rests are not predisposed to tumour formation. They are merely not immune

* There is, therefore, no need to fall back upon a *vitium primæ formationis*.

to it. This property they share with all the tissues of the body.

Since tissue malformations are not in any way predisposed to tumour formation, the evidence relied upon by the upholders of Cohnheim's theory to prove that all, or at least the majority of neoplasms, arise in cell-rests falls to the ground. Cohnheim's theory fails.

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THE CLINICAL FEATURES OF GROWTHS OF THE KIDNEYS

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In this paper the points upon which it is desired to lay special emphasis in connection with growths of the kidney are as follows:

1. When an operation is performed, it is important that not only the kidney should be excised, but the perinephric tissue should be removed as freely as possible, and the pedicle of the kidney ligatured and divided as near its origin as possible.

2. The series of growths analysed in this paper, eighty-one in number, attack more frequently the right side than the left in the proportion of 4 to 3, thus confirming anatomical and pathological observations recorded already by me [1] with regard to lesions other than growths of the upper urinary tract.

3. Urinary symptoms may arise from a secondary growth of the kidney, the primary growth being situated elsewhere.

4. The chief points in connection with the diagnosis of growths of the kidney are described.

5. Difficulties in the diagnosis of the real origin of the disease may be increased by bladder complications.

The material which forms the base of this paper is derived from two clinical cases, which have occurred in my own practice, and, of vastly greater importance, from the post-mortem records at Guy's Hospital between 1890 and 1910, and the Victoria Hospital for Children between 1889 and 1912.

I.—The Clinical Cases

The history of the two clinical cases is known up to the present date, and an examination of the treatment carried out in each establishes certain rules in procedure which, I think, we shall do well not to neglect.

This being a clinical paper, and not one dealing with the pathology of renal growths, it is sufficient for us to know that there may be found in the kidney three types of tissue—

(1) Connective tissue, (2) renal epithelial tissue, and (3) suprarenal tissue, which is not infrequently found underneath the capsule of the kidney, and may extend by normal methods of growth into the adjacent kidney substance. Its pressure may be regarded as possibly an anatomical fault, but nothing more. Now any one of these three tissues may take on malignant characteristics, giving rise to—

(1) Malignant connective tissue tumours, or sarcomata; (2) malignant epithelial tissue tumours, or carcinomata; and (3) malignant suprarenal tissue tumours, or hypernephromata.

This classification of malignant tumours of the kidney will be found, I imagine, adequate. So long as the exact embryonic tissue which gives rise to the kidney is unknown, so long will there be difficulty in adding to or altering this classification.

The history of the two clinical cases will now be recorded.

Case 1. *Hypernephroma of the Kidney.*—Mrs. M., widow, aged 66, was a bright, healthy-looking woman, who had wasted somewhat during the past six months. She had had intermittent attacks of hæmaturia, in which tubular clots could be seen, as though they had been formed in the ureter. Whilst the attacks of hæmaturia were present she suffered very little pain, but when they ceased there was a dull aching pain in the right loin, which was only very rarely of a colicky nature. She gave a history of having had a tumour removed from her right breast some twenty years previously, and there was a scar about four inches long over the lower part of the right breast.

On examination of the patient a large swelling was visible in the right loin, extending from under the costal margin downwards and slightly forwards to the anterior superior spine. When palpated it gave one rather the impression of being a fluid swelling, as though it must be a hydronephrosis, but she said the tumour was larger than it had been and did not vary in size.

Attention was particularly directed to the possibility of the tumour being a secondary growth, following a primary growth in the breast. The very long interval without any sign of recurrence, and the fact that no other secondary growth could be discovered, rendered this improbable. A cystoscopic examination of the bladder was made, but the patient was not bleeding at the time; both ureteric orifices were normal in appearance, opened and closed with their usual regularity, and the stream of urine through them appeared to be normal. This last sign appeared to me to be very important, as it has been pointed out that, when the hæmaturia ceased, lumbar pain became more pronounced, and therefore one might

assume that there would be some obstruction to the normal flow of urine during the painful periods, permitting neither the passage of normal urine nor of blood. This assumption was negatived by the cystoscopic examination. A diagnosis of enlargement of the kidney due to growth was made, and the question as to whether it was primary or secondary was left open. The fact that it had developed more than twenty years after the first operation led me to believe that, even if it were secondary, its removal was justified.

I therefore operated upon the patient on September 17, 1920. She was laid upon her left side, and a firm support was placed under her body. I made the incision which I usually make for exploration of the kidney, one reaching from the angle which the erector spinæ forms with the twelfth rib, downwards and forwards, to one inch above and in front of the anterior superior spine. The muscles were divided along the whole length of the superficial wound. The quadratus lumborum was identified; I usually refrain from cutting this muscle, but keep its incision in the wound, as a reserve in case I want more room for manipulation. After identification of the peritoneum, the perinephric tissue was incised, and the kidney isolated and drawn into the wound. It was found to be large, but the enlargement presented itself as a round swelling in the kidney about four inches in diameter—smooth and giving the impression of being a hydronephrosis after all. The swelling was incised, however, and found to be solid. The kidney was excised after ligature of the renal pedicle and division of the ureter. The patient suffered very little shock and was discharged fit and well four weeks after the operation.

Mr. R. Davies Colley reported that the growth was a hypernephroma, and the specimen is mounted in the Guy's Hospital Museum. The kidney is normal in appearance at the upper and lower poles, and along the whole of the inner border, except at the upper part of the hilum, where the tumour lies around but apparently has not invaded the pelvis of the kidney. It forms a well-marked projection on the outer border of the kidney. On section it is circular, and measures four inches across; it bulges from the cut surface of the kidney; it is whitish in colour, and shows softening areas, but no sign of suppuration.

In March, 1922, the patient presented herself for examination. The wound was soundly healed, but she complained of some pain. I saw her again in July, 1922, when a large swelling, hard, painful, and tender, could be felt under the scar. She also had a secondary deposit over the right frontal region.

Mr. C. H. Fagge saw her in consultation, and we agreed that nothing further could be done. In October, 1922, Dr. Shackleton of Watford reports that she is losing ground; both swellings have increased in size, and there is evidence of pressure upon the brain.

Case 2. A female, married, aged 30, was admitted under the care of Dr. Beddard for hæmaturia on January 25, 1921. I am indebted to him for permission to make use of the notes about her, whilst she was under his care. In September, 1920, she noticed that her urine was dark red, but the next day it appeared normal again. She had no pain. Fourteen days afterwards, after her menstrual flow, the patient noticed that her urine was very dark red, but the normal colour again returned in twenty-four hours. After the next menstrual flow the patient again passed dark red urine, which was very thick. During this attack she had extreme pain in the left side. The urine seems to have regained its normal appearance, but only for five days, when she had another attack of hæmaturia for twenty-four hours, but with no pain. She noticed nothing further till about a week before Christmas, when she had another period, after which her urine again became very dark red. She had no pain during this attack, but when the hæmaturia ceased after twenty-four hours, she had so much pain that she could hardly walk, and she could not lie upon her left side for several days. She then remained quite free from pain until her next menstrual period, beginning about January 18, 1922. The flow ceased on January 22, and the next day the urine was again dark red: the hæmaturia continued till the date of her admission.

On admission the patient felt quite well and complained of no pain. She looked rather puffy about the face. I could not satisfy myself as to palpability of the kidney. The urine was dark red with a specific gravity of 1023. It contained many red cells, no casts, some pus cells in excess of leucocytes of blood, and albumin in excess of blood. No tubercle bacilli could be detected. The x-rays showed no opacity to suggest calculus in the urinary tract, and the outline of the kidney was normal in size and position.

Irrigation before a cystoscopic examination had to be frequently repeated before the fluid in the bladder ran away clear, this pointing to a renal origin of the bleeding. The left ureteric orifice was somewhat crateriform and blood-stained; it did not appear to open and close regularly, and when open no fluid appeared to be discharged. The right ureteric orifice was normal in appearance and activity.

A catheter was passed 15 cms. along the right ureter without

difficulty; a good deal of urine was collected. The left ureter was then catheterised, but no fluid of any kind escaped. This second step was repeated in ten days' time, but still no fluid came down the left ureter.

Examination of the urine collected from the right kidney showed no pus, and no albumin apart from a little blood present. The urea percentage was 0·047, but this was considered to be normal for the dilution. The urine remained sterile at the end of seventy-two hours' incubation. A diagnosis of growth of the kidney was made in the medical wards. The patient was transferred under my care, as the original symptoms were still present, and Dr. A. P. Beddard and Dr. J. H. Ryffel considered that the right kidney was doing its duty.

The most striking points in the history are—

(1) the occurrence of bleeding from the urinary tract in relation to the menstrual flow; for this I am not prepared to offer any explanation;

(2) the occurrence of pain, not during the hæmaturia, but after it, as if the bleeding may have relieved congestion of the kidney;

(3) the absence of urinary secretion from the left kidney, as indicated by the cystoscopic examination;

(4) the apparently normal functional value of the right kidney.

By a similar operation to that described in connection with Case 1, I removed the left kidney without difficulty on March 26, 1921. The patient made an uneventful recovery without any evidence of shock, and was discharged apparently well. On splitting the kidney for the purpose of examining it, the condition appeared to be a pyonephrosis. No calculi and no growth were found. It was not deemed necessary to examine it further. This was a great mistake, as the future history will show.

At the end of November, 1921, the patient attended my Out-Patient Department, complaining of a small lump having formed in the wound. This was globular, and freely movable, and apparently about 1½ inches in diameter. Mr. V. E. Lloyd thought the swelling grew larger during the next two or three months, so, on March 10, 1922, my dresser, Mr. Pot, removed it. It was found to be a definite growth, encapsuled and very vascular, and in naked eye appearance rather suggestive of a secondary deposit following a papilloma of the bladder. As we know that papillomatous growths may occur in the pelvis of the kidney, I thought that there might have been such a renal papilloma present to explain the original pyonephrosis and the recurrent growth, the first by obstruction to the flow of urine, and the

second in the way that papillomata may behave after apparent removal. The growth was examined histologically and was reported to be a papillary carcinoma.

The further history of the patient is interesting. Shortly after her discharge from the hospital after the second operation she presented herself again at Out-Patients. There was a lump about the size of a hen's egg situated in the position which is usually occupied by the pelvis of the left kidney. After some observation it was felt that, as the lump was increasing in size and was the only swelling to be palpated, and was therefore presumably isolated, it would be well to remove it. In July, 1922, I made an incision near to the site of the old one and explored the swelling, which was found to be adherent to the aorta. It was removed by careful dissection, and was found, like the first recurrence, to be encapsuled and to present the naked-eye appearance of a recurrent papilloma. It was examined histologically and reported to be a papillary carcinoma.

I examined the patient again in September, 1922, and could find no evidence of any recurrence. There can, I think, be no doubt that in this case the original pyonephrosis was due to a malignant condition which was not obvious to the naked eye. The recurrences were due to local deposit in the region of the wound.

It may be laid down as an axiom from a perusal of these cases that a nephrectomy for any growth of the kidney should be associated with wide removal of the perinephric tissue, and ligature of the pedicle as near its origin as possible, so as to include in the excised part those lymphatic glands which are known to lie in the region of the hilum of the kidney. In neither case were these steps taken. My objections to removing the pedicle as near its base as possible in nephrectomy for non-malignant disease depend upon the presence of a small artery, the inferior capsular, passing from the renal artery to the suprarenal capsule. Although a small artery, it fulfils two important functions. It is the largest of the three arteries which supply the suprarenal capsule on each side. When we know a little more about the functions of the suprarenal bodies, we may be in a position to cut off a portion of its blood supply, by ligature of the pedicle of the kidney on the proximal side of the origin of the inferior capsular artery. The second function may be regarded as mechanical. If a pedicle which has been ligatured on the distal side of the origin of the artery be examined, it will be seen that the clot of blood which is formed in the renal artery extends back only so far as the origin of

the inferior capsular artery. If this artery were not in the position that it is, there would be no reason why the clot should not extend back to the aorta. In certain septic cases calling for removal of the kidney, this point is not without importance. In a case of excision of the kidney for a growth it is necessary to ligature the renal pedicle as near its base as possible, in order that we may be sure that the lymphatic glands in the neighbourhood are removed, and for this reason we may sacrifice the inferior capsular artery, its sacrifice being of less moment than the failure to remove lymphatic glands, which may be already invaded by malignant disease.

II.—The Post-mortem Records

I shall now proceed to a short analysis of the post-mortem cases of renal growths which were found at Guy's Hospital and the Victoria Hospital for Children during the years already mentioned.

The cases number eighty-one.

1. Primary growth of right kidney. 15 cases.

7 males	8 females.	
2 males	4 females	Sarcoma.
0 males	2 females	Carcinoma.
0 males	2 females	Hypernephroma.
5 males	0 females	Not stated.

2. Primary growth of left kidney. 11 cases.

8 males	3 females.	
2 males	1 female	Sarcoma.
1 male	0 females	Carcinoma.
2 males	0 females	Hypernephroma.
3 males	2 females	Not stated.

3. Primary growths in both kidneys. 3 cases.

2 males	1 female.	Sarcoma.

4. Secondary growths in right kidney. 14 cases.

10 males	4 females.	
2 males	1 female	Sarcoma.
8 males	2 females	Carcinoma.
0 males	1 female	Not stated.

5. Secondary growths in left kidney. 12 cases.

8 males	4 females.	
3 males	1 female	Sarcoma.
5 males	3 females	Carcinoma.

6. Secondary growths in both kidneys. 18 cases.

12 males	6 females.	
5 males	3 females . . .	Sarcoma.
6 males	1 female . . .	Carcinoma.
1 male	2 females . . .	Not stated.

7. Involvement by spread of growth of right kidney. 5 cases.

3 males	2 females.	
3 males	0 females . . .	Sarcoma.
0 males	1 female . . .	Carcinoma.
0 males	1 female . . .	Not stated.

8. Involvement by spread of growth of left kidney. 3 cases.

1 male	2 females.	
0 male	1 female . . .	Sarcoma.
1 male	1 female . . .	Carcinoma.

In one case, a male with sarcoma, the side is not stated.

These figures may be considered as regards age-incidence, sex-incidence and side-incidence.

Age-incidence.—The only point I would lay stress upon is that, although growths occur in every period from the first to the seventh decade, they are decidedly uncommon between the ages of ten and thirty. Between these ages there are only four cases, two of which fall under the head of bilateral renal sarcoma, and one of which may be rejected, as it was a case of involvement of a kidney in general sarcoma. I have no records of a case whose age was between eighteen and thirty.

Sex-incidence.—Males are more frequently affected by primary growth of the kidneys than females (17 : 12). Males are more frequently affected by secondary deposits in one or other or both kidneys than females (2 : 1).

Side-incidence.—The results of this investigation show clearly that, as with renal calculus and renal tuberculosis, the right kidney is more commonly affected than the left, as shown in the following table.

Primary growths	Right 15	Left 11
Secondary growths	,, 14	,, 12
Involvement by spread of growths	,, 5	,, 3
	Total 34	Total 26

These figures appear to demonstrate that the right kidney is affected by all clinical varieties of growth more frequently than the left in the proportion of 4 to 3.

In my paper, published in the *Transactions of the Medical Society*,[1] I showed that from the same records, with the addition of some at the London Hospital, both calculus and tubercle affected the right kidney more frequently than the left. The relative frequency of right renal tuberculosis, as compared with left renal tuberculosis, is 13 to 5. I adduced anatomical reasons for this relative frequency. The main reasons were the crossing of the right ureter by the root of the mesentery, and the greater angle at which the right ureter crosses the iliac vessels than the left; I have seen the right, but never the left, common iliac artery grooved by the ureter. I also brought forward pathological proof of retention and clotting of blood in the right renal pelvis, but not in the left, both kidneys being affected by the same general disease which led to the death of the patient. I am indebted to Professor E. Barclay Smith for information relative to the aortic glands. He tells me that they lie much more in relation to the right than to the left ureter. I should consider this observation to be of more value than any of mine, and distinctly confirmatory of them. We may then assume that there is more obstruction to the passage of fluid along the right ureter than along the left, and that as a consequence the kidney of the right side is more likely to be affected by calculus and tuberculosis than the left kidney. Now the proportion of growth in the right kidney as compared with growths in the left kidney is 4 to 3. Calculus, tuberculosis and growth are therefore all found more frequently on the right side than the left.

In addition to the incidence of growth of the kidney as regards age, sex and side, other important lessons may be learnt from these post-mortem records.

(1) A growth of the kidney may give rise to symptoms of renal disease, although it may not be primary but secondary, and in this type of case careful examination is necessary in order to discover the primary seat of growth. Two illustrative cases are now recorded.

Case 1. *P.M. Reports, Guy's Hospital*, No. 355, 1905.—A male, aged 58, was admitted for symptoms pointing to disease of left lung. A tumour was felt below the twelfth rib on the left side, and there was hæmaturia. P.M. large growth in right lung, smaller growth in left lung; right kidney good save for one small nodule of growth; left kidney showed a growth eight inches across in the upper two-thirds; necrotic on section. The calyces were filled with gelatinous-looking material, continuous with the growth but not invading the kidney.

Case 2. *P.M. Reports, Guy's Hospital*, No. 389, 1902.—A female, aged 62, was admitted suffering from difficulty and

pain in micturition, and hæmaturia. Post-mortem examination revealed primary carcinoma of the bile ducts of the liver, with a secondary cancer of the left kidney.

(2) A growth may invade the pelvis of the kidney from without and may grow down the ureter and project through its orifice into the bladder. Symptoms of bladder disease may thus be set up and the real origin of the disease be missed. This point will receive further attention when the symptoms of growth of the kidney are considered.

Symptoms of Growth of the Kidney

As in cases of growth occurring elsewhere in the body, carcinoma and other forms of growth of the kidney may give rise to no symptoms of the disease, and the condition may be only discovered after death. Such cases, if we except secondary deposits, are, however, very rare and need not now be considered. Pain, hæmaturia and the presence of a tumour may be regarded as the important symptoms of renal growth. There is sometimes a doubtful history of injury before the symptoms are noticed, but, as elsewhere, injury may direct the attention of the patient to the part affected. This history of injury appears to be more common with sarcoma than with other forms of growth.

Pain.—This may be a dull, aching pain confined to the back in the dorsi-lumbar region, or to one loin. Occasionally it may be more severe and more extensive, radiating into the groin of the same side. Or there may be cramp-like pains over the front of the thighs.

Hæmaturia.—This comes on suddenly and continues for some time. It may be very severe. When hæmorrhage is sufficiently severe to cause anxiety and to call for immediate operative treatment, it should always be regarded as having a renal origin. Hæmorrhage from a bladder tumour may be very severe, but in my experience it is never enough to be a direct indication for operation.

Clotted casts of the ureter and pelvis of the kidney may be passed through the bladder and urethra. The clots may, however, be retained in the bladder and lead to obstruction to the passage of urine and consequent retention. This I believe to be not at all common with vesical growths, except in the very latest stages, when failure of the bladder muscle, through general exhaustion, has occurred. Thus retention, with a large amount of blood in the urine, should make one suspicious of a renal tumour, and occasionally the bladder is opened for such a condition.

A case from the Guy's records (*P.M. Reports, Guy's Hospital*, No. 213, 1903) may be quoted in this connection. It is recorded as a hypernephroma of the left kidney occurring in a male whose age is not stated. He was admitted with retention of urine following hæmaturia, with formation of blood clots. Catheterisation followed by suprapubic cystotomy was performed, but the man died six days after admission. I think we may assume that the hæmorrhage must have been very severe. Nor was it a large growth of the kidney, for it is recorded that it was only 4 cms. across; it was spherical in shape, and projected into the pelvis of the right kidney. The growth was hæmorrhagic, and bleeding had taken place into the pelvis of the kidney, thence down the ureter and into the bladder.

The immediate symptoms of hæmorrhage may be arrested by such measures as were taken in this case, especially if the bladder be irrigated with very hot Liquor Hamamelidis; but the real origin of the bleeding must not be overlooked, and examination of both kidneys should be made. This masking of the real origin of the bleeding by symptoms pointing to bladder trouble, in cases which are in fact renal, reminds us of the masking of the symptoms of renal tuberculosis by cystitis. The conditions are, however, rather different in the two diseases. In renal growth the bladder symptoms are due as a very general rule to bleeding taking place into the bladder, and only very rarely to spread of the disease from kidney to bladder. In tuberculous disease, on the other hand, the bladder symptoms are always due to spread of the disease from the kidney to the bladder. Pain and hæmaturia may be associated together: the pain, owing to the formation of clots high up in the urinary passages, may be of a colicky nature; but very often pain and hæmaturia seem to alternate with each other, as is shown very well in the account of my second clinical case. When the hæmaturia occurs the renal pain may be less, and when the hæmaturia ceases there may be more renal pain. The hæmaturia may relieve congestion, and is evidence that the urinary passage has been freed for the transmission of urine and blood. The absence of hæmaturia is no indication that the urine is flowing, and therefore obstructive symptoms may be set up during the absence of hæmaturia.

Tumour.—A swelling in the renal region with resonance over it is frequently the first sign of renal tumour. This swelling may be very large, and extend into the skeletal pelvis, and to the level of Poupart's ligament. If such a large swelling is formed, hæmaturia is frequently a late symptom. It is worth

while examining the urine in these cases for sarcoma or carcinoma cells, which are often found in the urine with a renal growth.

Occasionally a swelling of moderate size may not be detected during life. Such a clinically impalpable tumour may be situated in the upper half of the kidney, so that if the kidney is in the normal position it cannot be felt.

Having now considered briefly the cardinal symptoms of growth of the kidney, we may pass to further symptoms. These may be classified under the heads of—

(1) Pyrexia;
(2) Involvement of other organs and structures;
(3) Septic changes supervening on the malignant condition;
(4) Localising and other symptoms, which are elicited by means of the cystoscope.

Pyrexia.—It is well known that the formation and growth of a sarcoma anywhere in the body may be accompanied by pyrexia; consequently kidney growths, especially sarcomata, may be associated with quite a high intermittent temperature reaching, it may be, to 104° F.

Involvement of other organs.—The intestines may be pushed forward and displaced by growth. Matting together of the intestines may take place, and patients with renal growth may thus suffer from and be subjected to an operation for intestinal obstruction. Thus a female (*P.M. Reports, Guy's Hospital*, No. 198, 1909), aged 40, was admitted into Guy's Hospital with serious symptoms of intestinal obstruction. An operation was performed, and a large right kidney was found. The patient, owing to her very serious condition, died soon after the operation. The right kidney was found post-mortem to be very large, the lower pole reaching to the brim of the pelvis. The lower two-thirds of the kidney were soft and friable and showed patches of firmer white material. The tumour was regarded as a carcinoma.

The liver may be involved in at least two ways. It may be the seat of secondary deposits, in which case it may be very much increased in size. It is very difficult in cases of right renal growth to be always certain as to what part of the swelling is formed by the liver and what part by the kidney. Or the liver may be moved away from its original position bodily, or by rotation on one or other of its axes. Frequently the two movements are combined. The spleen may also be displaced. The other kidney may be involved by secondary deposits.

In young children it is well known that both kidneys may be affected at the same time by sarcoma. The other kidney

may be the seat of compensatory hypertrophy. In my experience when a kidney, which is the seat of compensatory hypertrophy, is palpable, it is tender. The abdominal, inguinal, supra-clavicular and bronchial glands may be affected. The spine and ribs may also be involved.

Thrombosis of the renal veins and spread of the growth into the thrombus is not uncommon. Thrombosis may also spread into the inferior vena cava, leading to swelling of the lower limbs and engorgement of the superficial abdominal veins. If the tumour be removed, as we see from the clinical cases, recurrence may take place in the scar.

Septic changes supervening on the malignant condition.—An early condition of this may be shown by slight dilatation of the pelvis of the kidney, with accompanying congestion of the vessels and projection of the growth into the urinary passages. A later condition, in which there was well-marked pyonephrosis, is recorded in my second clinical case. The occurrence of secondary septic changes increase the pain, which has already been noted as one of the cardinal signs of tumours of the kidney.

Involvement of the bladder.—It occasionally happens that a primary growth of the kidney may project into the urinary passages and emerge through the ureteric orifice as a polypoid mass, where it may be seen with the aid of the cystoscope. I have not succeeded in finding such a condition described in the post-mortem reports at Guy's Hospital, but there are two cases reported, which may serve to show that such a condition might be secondary, not to a primary renal growth, but to primary disease elsewhere involving the upper part of the urinary system.

A female (*P.M. Reports, Victoria Hospital*, No. 66, Vol. IV.), aged 5 years, was found post-mortem to have a sarcoma of the mesenteric glands, compressing the stomach and intestines, and two cysts in the omentum, one of which pressed upon the upper part of the left kidney which it had faceted. The right kidney was normal. The left kidney was half as big again as usual. Secondary growths spread along its hilum and the pelvis was occupied by soft red substance.

In this case the original growth had started in the mesenteric glands, and had spread into the kidney along the hilum. We have therefore here an illustration of the upper part of the urinary tract being invaded.

A male (*P.M. Reports, Guy's Hospital*, No. 396, 1891), aged 46, was admitted into Guy's Hospital for hæmaturia of four months' duration, and much pain over the liver and thighs. A tumour was found in the right lumbar and umbilical regions. Spindle and round cells were present in the urine. The patient

rapidly emaciated and died. Post-mortem a round-celled sarcoma originating in the aortic glands was found. The growth involved a great part of the abdomen; it had invaded the duodenum viâ the duct of the pancreas, and had involved and entered the ureter at the pelvis of the kidney, down which it had grown and presented as a polypoid mass through the right ureteric orifice into the bladder. In this case the growth, which had entered the ureter in the region of the pelvis of the right kidney, had actually projected along this tube into the bladder.

Cystoscopic examination.—A cystoscopic examination to be of full value should be performed during an attack of hæmaturia, provided that the patient's general condition does not contra-indicate such examination. If the patient's condition is not too bad, the necessary irrigation of the bladder with hot fluid as a preliminary to cystoscopy may do good, as I have repeatedly noticed even in cases of severe hæmorrhage from the kidneys, so that it cannot be often that a cystoscopic examination is contra-indicated during an attack of hæmorrhage. A difficulty with cystoscopy for renal hæmorrhage is, however, this: it is very difficult for the bladder fluid to be quite free from blood. The necessary examination of both ureters has to be carried out quickly, and it may be quite impossible for any one but the chief examiner to see from which ureter the bleeding is taking place. I have reason to believe that many people think that a cystoscopic lamp is a half-watt electric bulb, and that it should render a sanguineous fluid clear and translucent. As a matter of fact a cystoscopic lamp, if new, is usually fused by a battery, having the E.M.F. of the common pocket torch, say four volts, and a cystoscopic lamp does not of itself cause an opaque fluid to become translucent. In many cases, however, the source of the bleeding may be detected and blood seen coming through one or other ureteric orifice. As a rule a catheter may be passed along the affected ureter, and the fluid, if any comes along, may be examined microscopically. The passage of a catheter along the ureter in the case of a renal growth is very different from the passage of a catheter along a ureter which is associated with tuberculous disease of a kidney. In this case, as a rule, in my experience, a catheter cannot be passed along the affected ureter. The other ureter should be examined visually, and the urine collected and examined by means of a ureteric catheter.

In combination with the cystoscopic examination the various functional tests of renal efficiency may be carried out. The cystoscopic examination of these cases would demand more

space and time than can be here spared, so I shall postpone the consideration of this important method of examination to a future paper.

Conclusions and Summary

In this paper I have attempted to show, first, that in all cases of nephrectomy for growth, the perinephric tissue should be excised as widely as possible and the renal pedicle left as short as is consistent with safety.

Secondly, that renal growths resemble calculus and tuberculosis in affecting the right kidney more frequently than the left.

Thirdly, that urinary symptoms may arise from a secondary growth of the kidney, the primary seat being elsewhere.

Fourthly, points in diagnosis gathered from post-mortem records have been described.

Fifthly, that difficulties caused by bladder complications may arise in the diagnosis of renal growth.

REFERENCE

[1] A. R. Thompson: *Trans. Med. Soc. of London*, xxxvi, 328, 1913.

THE TREATMENT OF COMPLETE OBSTRUCTION OF THE COLON

By R. P. ROWLANDS, M.S., Surgeon to Guy's Hospital.

THE best way of dealing with obstruction due to carcinomatous strictures of the colon is still a subject for debate, there being no unanimity amongst surgeons. Whenever possible the onset of complete obstruction should be prevented, but unfortunately this is not always practicable, for complete stoppage is the first noticeable symptom in a few cases, and in others the significance of premonitory signs is too often not appreciated by the patient and his attendants. In a patient over thirty years of age increasing constipation or constipation alternating with spurious diarrhœa, offensive stools, intestinal flatulence and griping pains should arouse suspicions of carcinoma of the colon. Wasting, anæmia, the constant presence of occult blood in the stools, with or without the passage of obvious blood and mucus, should drive us to examine the rectum and colon very thoroughly and without delay. Bimanual examination of the pelvis and loins may discover the growth. Sigmoidoscopy and radiography after an opaque meal or preferably a barium enema are very valuable, often locating the obstruction, but they are far from infallible. When grave doubt still exists, an exploratory laparotomy should be recommended, as it may prevent overlooking a growth until it becomes irremovable or complete obstruction develops. Under these quiescent conditions the growth can be removed and the natural channel re-established at one operation. The advantages of this to the patient are numerous and of incalculable value, the immediate and ultimate prognosis being extremely favourable.

It is not very difficult to diagnose complete obstruction of the large intestine. Purges and enemata fail to act, and the abdomen becomes more and more distended and tympanitic but not rigid or tender. The temperature is subnormal. The distension is much greater than that caused by obstruction of the small intestine, and one or both flanks are filled out according to the site of the stoppage. The condition is usually not so urgent as obstruction of the small bowel, and there may

be time and opportunity to carry out some or all of the examinations already mentioned.

In many cases, however, the surgeon is not consulted until the obstruction has existed for many days, and the condition has become urgent with great distension of the abdomen. Under these circumstances it is quite impossible to make an exact diagnosis and especially to locate the obstruction.

Although carcinoma is by far the commonest cause of obstruction of the large bowel, it should not be forgotten that other causes exist, such as volvulus of the cæcum or pelvic colon, intussusception, gall-stones or enteroliths impacted in the pelvic colon, and bands across the colon, notably at the splenic or hepatic flexure or the pelvic colon. Diverticulitis also may cause bands or tubular stricture of the pelvic colon. It is also important to bear in mind that some forms of obstruction of the small intestine may be mistaken for obstruction of the colon; under these circumstances both the ascending and descending colon have been exposed and found empty, showing the need of a median exploratory laparotomy in most cases of intestinal obstruction.

(A) Medical Treatment

In some cases of impending or complete obstruction of the colon due to carcinomatous stricture, enemata may overcome the obstruction and tide the patient over his acute peril. Solid fæces blocking the stricture may be thus dislodged and a large collection of liquid fæces together with gas evacuated. Soon the temporary inflammatory swelling round the stricture may subside. In this way cæcostomy and colostomy may sometimes be avoided, and a cure made at one operation to the great advantage of everyone concerned. In grave cases, however, time must not be wasted in this endeavour. If two enemata fail to act well it is best to proceed at once to operation. Repeated purges and enemata are futile and dangerous.

(B) Surgical Treatment

(1) *Cæcostomy*

In very grave cases, when the greatly distended cæcum may be recognised during peristalsis, cæcostomy, as recommended by Sir Harold Stiles,[1] is ideal. It can be performed very quickly under local or general anæsthesia and is attended with very little shock. When the patient has got over his acute obstruction further examinations can be made to locate the

latter, and perhaps a radical operation undertaken, the cæcostomy being allowed to close later. I do not adopt this as a routine method, because it may fail to save life in some of the cases already mentioned, where the obstruction is not caused by carcinoma of the colon, and because it does not deal satisfactorily with irremovable growth and does not complete the diagnosis and enable us to decide if a secondary radical operation is possible.

(2) *Right Paramedian Exploration*

Except in grave cases, very old, feeble patients, or where the diagnosis of growth is certain, I prefer to explore through a right paramedian low incision, the rectus being displaced outwards. A third of the five-inch incision is above and two-thirds below the umbilicus. The opening in the peritoneum is made only just large enough to admit a folded hand, so that there may be no fear of prolapse of the distended intestines. The hand seeks the cæcum; if this is full the obstruction is in the large intestine and the hand is at once passed to the left, where the obstruction may be found in the pelvic colon or the rectum. If, however, these are normal and not distended, the hand passes up the descending colon to the splenic flexure and along the transverse colon, until the obstruction is encountered. It is important to locate the obstruction and to ascertain its nature, and this can be gently done with but little danger or disturbance.

If a growth is found, its immediate removal is too dangerous an operation, carrying a mortality of over 90 per cent., but the possibility of removal at a later date can now be settled. The hand, therefore, must examine for adhesions, especially to vital structures, and must also be passed above and below the liver to examine it for secondary growths. It is also important to feel for secondary growths in the peritoneum, especially in the pelvis. Should the growth be irremovable, there is no great advantage in doing a cæcostomy, which is not a good method of permanently draining the colon, the stools being too frequent, liquid and irritating, but a colostomy is at once performed in the most advantageous position, having regard to the position of the particular growth. If, on the other hand, the growth is removable, some means of temporary drainage of the colon must be adopted, leaving the resection to a more favourable opportunity. This drainage is urgently necessary to save life, and with this object always in view cæcostomy, colostomy, short-circuit or Paul's method may be chosen, the choice depending on the special needs and condition of each particular patient.

(i) *Cæcostomy.*—There is no doubt that this provides the quickest, safest and most thorough drainage of the distended colon. It drains the bowel low down and at the point of meeting of two currents—the one from the small intestine through the ileo-cæcal sphincter, which is still effective, and the other from the whole length of the colon backwards by reverse peristalsis. The result of the meeting of these two currents in the thin-walled cæcum is that this part of the bowel often becomes greatly distended and even paralysed, with secondary kinking at the hepatic flexure and with greater risk of rupture here than anywhere else. Drainage at the lowest point of this retort-like paralysed sac affords very prompt and adequate relief.

The median wound is rapidly closed in layers and sealed. A small grid incision is made over the cæcum and its lower and external pouch is gently withdrawn, emptied back and clamped with a soft intestinal clamp. If the whole cæcum is delivered it may rupture. It is then packed off and incised, and a soft rubber tube, having an internal diameter of one-quarter of an inch and two side holes close to the end, is inserted and fixed in with a single catgut suture piercing the edges of the small cæcal incision. The tube and incision are then invaginated with three purse-string sero-muscular sutures of catgut, thus making an " ink-bottle " cæcostomy. The cæcum is replaced in the abdomen, sewn to the peritoneum and muscle, and the parietal wound is closed round the tube, which is securely stitched to the skin. This method is far better than simple incision of the cæcum or tying in a Paul's tube, which generally leads to sloughing and leakage within three or four days. The rubber tube drains comfortably for two or three weeks or more without infection of the parietes, and, when it comes out, the valve is generally so efficient that no leakage occurs on to the skin. In fact the tube has to be quickly replaced to prevent the cæcostomy healing. As a general rule the secondary resection can be undertaken in anything from ten days to four weeks after the preliminary operation. The cæcal contents, being liquid and gaseous, drain easily through the rubber tube, through which the bowel can also be washed out and normal saline and glucose solution administered, if necessary.

(ii) *Colostomy.*—Colostomy may be more advantageous when permanent drainage is required on account of the growth being irremovable, and also when there is much local distension above a removable growth in the pelvic colon. Under these circumstances the colostomy is made near the growth; it is subsequently removed with the growth and an end-to-end union is made, a rubber tube being then passed from the anus

through the anastomosis into the colon above, so that no over-distension can occur to strain the union or cause a leak, abscess, peritonitis or fistula.

(iii) *Short-circuit.*—In some cases with only moderate distension and no paralysis of the bowel, a short-circuit is better than either of the two methods already mentioned. A typical example is in the case of growth of the splenic flexure, when the middle of the transverse colon can be joined to the pelvic colon. Later on, the resection of the growth with blinding of the two ends near the anastomosis is a comparatively simple and safe operation, a good channel having been already established some weeks earlier. When a colic growth is irremovable, a short-circuit, if it be practicable and safe, is far more satisfactory to the patient than either cæcostomy or colostomy, for he is saved the misery of having an artificial anus.

(iv) *Paul's method.*—The method of Paul or Mikulicz is falling into disuse except in selected cases, chiefly because it is so tedious and generally calls for a second or even more operations before the patient is well. In this method the growth is withdrawn, packed off and removed, two Paul's tubes being tied into the open ends of the remaining colon. No attempt is made to join them end-to-end. Later the spur is removed by clamping, and later still the colostomy sinks in and closes spontaneously, or it is closed by operation. I rarely use this method now, preferring cæcostomy with secondary resection, but I have often used it successfully for carcinomatous obstruction of the pelvic colon. It has the advantage of being very safe, but it does not allow very free removal of the lymphatic vessels and glands, and complete recovery after it is very slow.

Conclusions

1. To prevent death from complete obstruction of the colon early and efficient drainage of the bowel is essential.

2. Cæcostomy is the simplest, shortest, surest and safest method of doing this.

3. An exploration, gently carried out through a separate paramedian incision to determine the site, nature and extent of the disease and the prospect of a radical cure at a later date, is very desirable, except in grave cases.

4. When the obstruction is due to irremovable malignant disease, either colostomy or short-circuit is better than cæcostomy.

5. Resection of a carcinoma of the colon, with restoration of the natural channel, is better deferred until the obstruction

has been satisfactorily overcome by drainage. Secondary resection is infinitely safer and can be undertaken from one to four weeks later, according to the local and general condition of the patient.

6. Whenever possible, complete carcinomatous obstruction of the colon should be anticipated, the diagnosis being made and the growth removed at one operation with the most satisfactory result.

REFERENCE

[1] Sir H. Stiles: *Brit. Journ. Surg.*, ix. 1, 1921.

A REVIEW OF SOME CASES OF NEOPLASM OF THE ACCESSORY NASAL SINUSES

By W. M. MOLLISON, C.B.E., M.Ch., Surgeon-in-Charge of Ear and Throat Department, Guy's Hospital.

THESE notes are based on eighteen cases of growth arising in the maxillary antrum or ethmoid cells treated in the Ear and Throat Department.

Growths of the accessory nasal sinuses used to be classed with growths of the upper jaw, whether arising from bone, periosteum, antrum, or teeth. Later, growths of the nasal fossæ and accessory nasal sinuses were grouped together. Perhaps it is now better to differentiate growths arising in the accessory sinuses from those of the nasal fossæ. The former spread to the nose and may present themselves as nasal growths, polypi, or ulcerations. Growths of the nose usually arise on the septum and can be separated entirely from the previous group, which invade the nose and are on the outer wall.

When the exact site of origin of antral and ethmoid growths is studied, difficulty is experienced. It is obvious that in some cases the lining mucous membrane of the antrum is the site, in others the ethmoidal cells, but in many cases it is impossible to decide at operation from which sinus the growth originated, or whether mucous membrane, bone, or periosteum was first affected.

Trantman [1] considered the antrum the commonest seat of origin of malignant growths of the upper jaw, while von Donogany [2] held that the middle turbinal was. Da Costa [3] speaks of sarcoma of the antrum, but it is not clear that in his cases the growth did not arise from periosteum. Binnie [4] mentions three cases of glandular carcinoma originating in the accessory sinuses, one case having metastases, and states that glandular carcinoma is much less malignant than squamous carcinoma.

Symptomatology

The typical symptoms of growth in the antrum are fairly constant.

Pain is always present and is often severe in character, preventing sleep. Its position is over the maxilla, in the temporal region, in the eye, behind the eye, or in the alveolus. It increases in intensity as the disease progresses.

Swelling of the face in some degree is frequent. The position varies; often it is infra-orbital, but in some cases the canine fossa is filled up; it may be most obvious over the nasal process of the maxilla, or again it may be best felt in the floor of the orbit.

Epiphora is sometimes an early symptom and is always present in the later stages.

Nasal obstruction is not constant, but is very frequent; it is due either to pushing in of the whole outer nasal wall or to malignant polypi, or to simple polypi in connection with suppuration in the antrum, a condition which is invariably associated with growth. Obstruction may be complete.

Nasal discharge is really the result of the obstruction; it may be mucous, muco-purulent, or purulent, and is often bloody.

Displacement of the eye is a most important symptom; in antral growths the eye is pushed upwards and perhaps slightly outwards; eye displacement in conjunction with swelling of the maxilla and pain makes the diagnosis of growth almost certain.

The picture drawn by a combination of the above symptoms leaves no doubt as to the diagnosis of growth of the antrum, or at least gives such strong evidence that the antrum must be opened and its lining investigated. This reservation is made because very occasionally conditions other than malignant growths occur in the antrum giving rise to exactly similar symptoms: two illustrative cases will be fully described under the heading of diagnosis.

Unfortunately the above picture is that of a fairly advanced case. The majority of cases do not come under observation till the disease is advanced; this is certainly true of hospital cases and to a great extent of private cases also. It is scarcely an exaggeration to say that a really early case of growth of the antrum or ethmoid is a rarity in most surgeons' experience.

Later in the disease, as the growth spreads, other symptoms are added to those given.

Palatal swelling is, as a rule, fairly late in making its appearance; this is fortunate, because removal of the palate at operation militates against recovery. Later this swelling ulcerates and may form a large mass in the mouth.

Swelling in the temporal fossa occurs at a late stage; it

indicates spread of the growth deeply into the temporo-maxillary fossa, and its occurrence is a contra-indication to operation.

Involvement of skin over the growth is one of the late signs; the skin over the most prominent part of the swelling becomes red and fixed to the deeper tissues; eventually it ulcerates. This involvement of skin does not contra-indicate operation, but it means that a large cavity will be left in the face, demanding a plastic operation later or some artificial filling of the cavity.

Glands may never be involved; certainly this is not an early manifestation. Their discovery in the neck need not make for a bad prognosis, as is proved by case 1; in this case a carcinomatous gland was removed at the operation for ligature of the external carotid artery, and the patient is still alive nearly nine years after.

To sum up the question of symptoms: swelling of the face combined with deep-seated pain of some weeks' duration and epiphora, all in a patient over the age of fifty, must lead to the strongest suspicion of growth in the antrum or ethmoid. If to these symptoms is added displacement of the eye, the diagnosis is certain enough to demand opening of the antrum through the canine fossa or face to obtain material for microscopical examination. Too often these cases are allowed to drift on under the impression that pain in the face or eye is connected with antral suppuration or with the teeth. The teeth can easily be eliminated as a cause, but it must then be remembered that chronic antral suppuration is never a cause of severe pain; on the other hand, antral suppuration is often a complication of growth, and indeed chronic suppuration in the antrum or ethmoid may lead to malignant disease of those sinuses.

Scudder,[5] in his *Tumours of the Jaws*, discussing symptoms of sarcoma of the upper jaw, lays stress on painful or loose teeth as an early indication, and also persistent neuralgia or bleeding from the gums after extraction of teeth. Two of my cases had been in the hands of a dental surgeon. Scudder also gives a list of symptoms of growth beginning in the antrum. The following is the list with my comments:—

Pain in the cheek: this has been found invariably.

Foul discharge from one nostril: very usual.

Bulging of the cheek: very common.

Fullness of the palate: only in late cases.

Swelling of the inferior turbinal: equivalent to pushing inwards of the outer nasal wall.

Tender face.

Repeated nose bleeding in the absence of antral suppuration : this symptom has not been met with.

Nasal polypi.

Epiphora : an early symptom in my experience.

Deafness : not noticed in this series.

Displacement of the eye : often seen.

Double vision, which may be the earliest symptom : not seen.

Diagnosis

As has been noted above, cases of growth of the antrum or ethmoid present a definite symptom-complex, and there are but few conditions that cause difficulties in diagnosis. Nevertheless there are conditions that give rise to some of the typical symptoms and demand consideration. The first and most frequent is *syphilitic periostitis of the superior maxilla.* The nasal process of the maxilla is the part usually affected, and a swelling occurs on the face in that position; the skin over it is reddened, pain is experienced, and there may be epiphora.

The swelling and redness localised to the part below the inner canthus should lead to the suspicion of periostitis; if in addition there is absence of nasal obstruction or discharge, some superficial disease is probable.

The finding of a positive Wassermann reaction or of other signs of syphilis, such as leucoplakia of the tongue or scars over the tibiæ, will greatly aid diagnosis. In cases in which the reaction is negative and in which the symptoms persist in spite of a short course of anti-syphilitic treatment, the antrum should be explored through the canine fossa, and if thickened mucous membrane be found, a piece removed for microscopical examination.

If the case is syphilitic, appropriate treatment is followed by rapid improvement. When the syphilitic periostitis occurs in the infra-orbital region and the floor of the orbit, the eye may be displaced upwards : fortunately anti-syphilitic treatment is most effective in these cases, causing rapid absorption of the swelling. Occasionally the upper or inner wall of the orbit is the affected part, and then the eye may be pushed downwards or outwards and downwards or even forwards.

Swellings of *dental origin* by causing swelling on the face and pain may lead to difficulty in diagnosis. It is recognised that pain in a tooth may be an early symptom of growth of the maxilla, and in two cases the writer has seen cases of carcinoma of the antrum, in which teeth had been extracted and the

root cavities treated for some weeks because the pain had continued. An x-ray examination of the skull in all cases of continued pain in the teeth will be of great value: this same x-ray examination will also help to exclude *dental cysts* and *odontomata.*

The *bony swellings of the maxilla* must be mentioned, but they do not often call for differentiation from growths of the antrum; they are of slow development, generally painless, and only in the late stages do they cause displacement of the eye. X-ray examination shows them to be of great density. *Leontiasis ossium* is to be included in this group. The rare cases of *exostosis* growing from the inner wall of the antrum may be mentioned, though they can scarcely be considered as giving rise to difficulty in diagnosis: in one historic case of Hilton's the exostosis grew to such a size that the eyeball was pushed out of the orbit and ruptured, the skin of the face sloughed, and finally the exostosis fell out and the patient made a good recovery: the exostosis is in the museum of Guy's Hospital. Hilton's paper, which appeared in the first volume of these Reports eighty-seven years ago, is reprinted on page 97.

Acute osteomyelitis of the superior maxilla may produce many of the symptoms of growth, but can never offer serious difficulty in diagnosis; the acuteness of the illness, the considerable rise of temperature, the recent development of the swelling and its rapid increase, the tenderness and œdema, all make the picture differ from the slow development of growth. It may be noted that this disease may occur in the course of a chronic antral suppuration, and is the only way in which chronic antral suppuration gives rise to swelling of the face; further, it is only certain forms of antral infection that lead to the acute complication.

On the other hand, sinus suppuration may be a complication of growth of the ethmoid or antrum: in all cases of growth, infection of the sinuses is found at operation; there is pus in the frontal sinus and antrum, and where the growth has spread backwards, there is invariably pus in the ethmoidal cells and in the sphenoidal sinus: occasionally this sinus suppuration may give rise to acute symptoms, and these symptoms may be so severe as to overshadow the previous symptoms due to the growth. One of the cases quoted below was a good example of this; the patient presented the appearance of an acute frontal sinus suppuration with sub-periosteal abscess or orbital cellulitis causing displacement of the eyeball. At operation the diagnosis was confirmed, but extensive growth of the ethmoid cells was found to be the origin.

In this series of cases two unusual conditions were found; one was a case of *osteitis fibrosa*, and the other a case in which the antrum was filled with inflammatory tissue, perhaps syphilitic. In neither case was diagnosis possible before operation; both patients presented many symptoms and signs typical of growth. Pain, swelling, displacement of the eye, nasal obstruction and discharge were present in both, and in the first swelling of the palate was added; the appearance at operation of the contents in the inflammatory case was so like carcinoma that operation for removal of the jaw would have been undertaken if preparations had been made.

Scudder mentions that there is no difference between early carcinoma and suppuration in the antrum.

The following cases presented difficulty in diagnosis from growth.

Case of Osteitis Fibrosa of the Superior Maxilla.—Mr. B., aged 39, was referred by Dr. Sells on account of swelling of the left side of the face, and was admitted to Barnabas Ward under the care of the writer. For some weeks the patient had suffered from pain in the left side of the face and a nasal discharge; latterly the hard palate had been swollen.

On examination the left side of the face was swollen, firm to the touch. The swelling extended from the infra-orbital margin to the alveolus. The eye was pushed slightly upwards. There was a smooth swelling of the left side of the hard palate yielding to pressure. Nasal examination showed marked obstruction and a purulent discharge, the obstruction being due to bulging inwards of the outer wall.

Though the man was only 39, the clinical picture was typical of growth of the antrum, and operation for removal was undertaken. Ferguson's incision was employed, and the maxilla exposed by turning out the soft tissues of the cheek: the anterior wall of the antrum was found bulging and the bone thinned. On opening the antrum a whitish mass was found filling the cavity completely and apparently in layers; the mass had destroyed the bone, by pressure probably, so that there was no hard palate left; the whole of the outer nasal wall was absent. The septum had been reached and pressed over to the right side, and the mucous membrane destroyed over a considerable area; the ethmoid and the floor of the orbit were also encroached upon. The mass was removed as cleanly as possible and the wound closed; the man made a good recovery and has not had any sign of further disease; it is now two years since the operation.

Dr. G. W. Nicholson reported " osteitis fibrosa."

Case of Expansion of the Antrum by Inflammatory Tissue.—Mrs. L., aged 46, was referred by Dr. Howlett in July 1920 on account of swelling of the left side of the face and pain.

On account of pain in the face a tooth was extracted four weeks before the patient's admission to the hospital, but without relief. On examination the left side of the face was swollen and the eye pushed upwards; the skin was puffy and the eyelids œdematous. There was left-sided nasal obstruction and discharge.

The possibility of some syphilitic condition was considered, but discarded on account of the displacement of the eye, and exploration of the antrum was advised.

The antrum was opened through the canine fossa: it was found to be filled with soft granulation tissue, which bled easily and was to the naked eye in all respects similar to the contents found in cases of growth. Some of the tissue was taken for section, and Dr. Nicholson reported it to be inflammatory.

A Wassermann reaction was strongly positive, and under anti-syphilitic treatment the patient made a good recovery and remains in good health more than two years later.

Such a case emphasises the difficulty of naked-eye diagnosis of growth and the importance of excluding syphilis as a cause even when clinical examination seems to negative it.

Pathology

Dr. G. W. Nicholson kindly examined and reported on most of the cases. The majority proved to be basal-celled carcinoma; the rest were columnar-celled, spheroidal-celled, squamous-celled, or mixed-celled carcinoma. Four were sarcoma, two of these small-celled chondro-sarcoma. The two latter were most malignant; recurrence rapidly took place, the patients dying ten months and two months respectively after operation. Basal-celled carcinoma gave the best prognosis. According to Scudder, the prognosis is worse for carcinoma than sarcoma.

In Gask and Wilson's *Text-book of Surgery* [6] tumours of the nasal fossæ and accessory sinuses are dealt with together: it is stated that sarcoma occurs in children and adults, and that prognosis is unfavourable. Carcinoma appears in two forms: (1) columnar-celled, probably originating in the ethmoid, and (2) squamous-celled, originating from the antrum or front of the septum, and the prognosis for this second type is much the worse. It is also noted that glands or metastases are rare.

The degree of malignancy is an important factor in cases of growth of the antrum and ethmoid: basal-celled carcinoma is the least malignant, while chondro-sarcoma is most malignant.

In my series of cases this was borne out. The cases of chondro-sarcoma developed recurrences and died in a few months. On the other hand, one case of basal-celled carcinoma

lived eight years, and indeed is still well without any sign of recurrence nearly nine years after operation.

In none of my cases were metastases met with, but the cervical glands were found infected in one case. It is usual to find two or three slightly enlarged glands over the carotid sheath at the operation for ligature of the external carotid artery, but these glands are not usually infected by carcinoma.

Treatment

All the cases in this series were dealt with by operation. Of eighteen cases one is alive and well nearly nine years after operation, one is free from recurrence eighteen months after, but the remaining thirteen cases that could be followed up died at periods varying from two days to twenty months after operation.

Diathermy was applied to the deep parts of the wound at the end of the operation in two or three cases; and in one case a radium emanation tube was inserted through the nose in the case of a recurrence of carcinoma antri.

Several cases were seen during the period covered by this series in which the disease was considered to be too advanced for operation, particularly those in which the skin of the face was extensively involved, the palate was ulcerated, the temporal fossa obviously filled up by growth or the eye much proptosed, suggesting extension to the base of the skull through the sphenoidal fissure. In such cases palliative treatment in the form of x-ray applications was employed.

Though the results of operation cannot be looked on as good, since recurrence was almost invariable, yet from one point of view operation justifies itself; the severe pain that prevents sleep is always relieved for a time at least, and in some cases permanently.

In no case was the disease seen at an early stage. In most cases the diagnosis offered no difficulty; pain, slight or obvious displacement of the eye, epiphora, unilateral nasal obstruction and swelling of the face made up the typical picture.

In one case the skin of the face was infiltrated, necessitating the removal of a large amount of the cheek; in one case (reported to the Laryngological Section of the Royal Society of Medicine in December, 1921) the disease was complicated by acute frontal sinus suppuration with an abscess over the frontal bone, and in one case a malignant gland was found in the neck while tying the external carotid, and the patient is well eight years after.

As far as could be decided the growth began either in the

antrum or ethmoid: in two cases a mass of growth was found in the sphenoidal sinus, and in one or two a process seemed to be invading the frontal sinus.

Technique of the Operation

In all cases anæsthesia was maintained by the intra-tracheal insufflation of ether, and in several cases Dr. Shipway kindly took charge of this most important part of the operation. Owing to the use of this method of anæsthesia, the operation could be performed without anxiety about entrance of blood into the air passages, and every stage could be carried out deliberately. This was particularly useful in the later stages, when the deep parts of the wound could be examined for extensions of growth and the sphenoidal sinus opened at leisure; this step was needed, as the sinus always contained pus and in some cases growth which had spread into it. It says much for this method that only one patient developed any lung infection after operation; she was 80 and the growth so extensive that the hard palate had to be removed.

In the majority of cases the external carotid artery was ligatured, and it seemed that in those cases in which that procedure was adopted the subsequent bleeding from the cheek was less than in the cases in which no ligature was used.

The incision was chosen according to the position of the apparent bulk of the growth. When the antrum was chiefly involved, Ferguson's incision was made, though it was not found necessary to cut through the lip in all cases. In some cases the lip was cut through, but the incision along the infra-orbital margin was omitted. To reach ethmoidal growths a modified Moure's incision was found admirable, giving plenty of room and leaving almost no scar; this incision begins internal to the inner canthus (in the usual position of an ethmoid incision), and is carried down and out over the face towards the lower border of the malar bone: should the frontal sinus require opening the incision is carried upwards under or through the eyebrow, as in a Killian operation. This incision allows of complete removal of the ethmoid and of most of the maxilla should the ethmoidal growth be found to have invaded it.

The soft tissues are now pushed aside to expose the maxilla, the orbital margin, and the floor of the nose; should the growth have come through the anterior wall of the antrum and involve the soft tissues of the face, the flap must be dissected well free of growth and even a very thin flap will survive.

By means of a gouge and hammer the bone is cut through (1) *below*, along a line parallel to the alveolar margin at the

TABLE OF CASES.

No.	Sex.	Age.	Disease.	Date of Operation.	Remarks.	Length of Life after Operation.
1.	F.	46	Carcinoma, L. antrum.	Jan., 1914	Secondary gland removed from neck, Dec., 1915.	Still alive and well.
2.	F.	19	Sarcoma, R. ethmoid.	Jan., 1915		Lost sight of.
3.	F.	19	Small-celled chondro-sarcoma, L. ethmoid and antrum.	Nov., 1914	Rapid recurrence.	Died in 2 months.
4.	F.	30	Basal-celled carcinoma, R. antrum.	Oct., 1915	Nodule removed from scar, May, 1916. Further recurrence in malar region treated by diathermy, Nov., 1916.	Died 1917, 15 months after operation.
5.	F.	44	Carcinoma, R. antrum.	Dec., 1915	Rapid recurrence.	Died in 4 months.
6.	F.	80	Carcinoma, R. antrum.	Feb., 1916	Hard palate involved and removed.	Died 2 days after operation.
7.	M.	63	Basal-celled carcinoma, R. antrum.	June, 1916	Recurrence in alveolus removed, July, 1917. Radium emanation tube inserted into further recurrence, Jan., 1918.	Died 20 months after operation.
8.	F.	40	Squamous-celled carcinoma, R. antrum.	Oct., 1916	Skin of face involved requiring removal.	About 12 months.
9.	M.	43	Carcinoma, R. antrum.	Nov., 1916		Few weeks.
10.	F.	58	Mixed-celled carcinoma, L. antrum and ethmoid.	Jan., 1921		10 months.
11.	F.	25	Chondro-sarcoma, L. antrum.	Jan., 1921	Rapid and extensive recurrence forming a very large swelling.	9 months.
12.	M.	43	Cystic basal-celled carcinoma, L. ethmoid.	April, 1921	Dura mater wounded at operation; good recovery.	At least a year.
13.	M.	48	Spheroidal-celled carcinoma, R. antrum and ethmoid, complicated by acute frontal sinusitis and subperiosteal abscess.	Aug., 1921	Contracted erysipelas; recovered, Jan., 1922, in infirmary with mental symptoms; died.	About 7 months.
14.	M.	60	Carcinoma, R. antrum.	Nov., 1921	Rapid recurrence.	3 months.
15.	M.	58	Columnar-celled carcinoma, antrum.	Aug., 1917		
16.	M.	60	Carcinoma, L. ethmoid.	July, 1917		
17.	F.	60	Carcinoma, L. antrum.	Aug., 1917		
18.	F.	56	Carcinoma, L. antrum.	June, 1922	Recurrence in 4 months.	

level of the floor of the nose; this cut is carried through to the nose (as in a Denker's operation). (2) *Externally*, the junction with the malar is divided; it is well to make this section as far as possible because it appears that recurrence is prone to occur in this direction. (3) *Above*, the nasal process is cut through; usually this region is so softened by growth that it is easier to tear through with bone forceps. The main mass of growth can now be levered out. Thereafter the outer wall of the nose is removed with the turbinates; the middle is usually infiltrated with growth; the floor of the orbit is removed if invaded and any growth found infiltrating the orbital tissues dissected free from the fat. It was not found necessary to remove the palate in the majority of cases, since even if the growth reached the floor of the antrum, it was not invading the bone. It may be noted here that in Case 1 growth was stripped from the antral floor and no recurrence followed.

The ethmoid is now removed widely; this exposes the sphenoidal sinus, which is opened freely, because it almost always contains pus, and in some cases growth is found invading it and filling it. Lastly, the deep part of the wound is examined for remains of growth; it is here that diathermy is useful. Sulphur is then powdered into the cavity, and the flaps are sutured.

In the case of primary ethmoid growths the ethmoid is separated above and below through the nasal process of the maxilla, and is removed by means of Luc's forceps or bone forceps. It may be necessary to follow the growth as high as the dura mater of the anterior fossa; indeed in one case the dura was exposed as far back as the sphenoid and wounded in one spot, with escape of cerebro-spinal fluid, but no ill effects resulted. The frontal sinus should be explored, since it almost always contains pus and requires to be drained.

The immediate after effects of operation are good; the patients suffer but little from shock and can in many cases get up on the third day. The deformity is very slight, and primary union is the rule. With the infra-orbital incision there is some œdema of the lower eyelid lasting a few weeks, but this disappears gradually.

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[1] Trautman: quoted by Scudder, *vide infra*.
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CASE OF
A LARGE BONY TUMOUR IN THE FACE
COMPLETELY
REMOVED BY SPONTANEOUS SEPARATION
TO WHICH ARE ADDED,
OBSERVATIONS UPON SOME OF THE
FUNCTIONS OF THE SOFT PALATE AND PHARYNX

By MR. HILTON.*

(Reprinted from Guy's Hospital Reports, Vol. I. p. 493, 1836.)

THOMAS MOORE, aged 36, is a well-formed man; and has enjoyed perfectly good health, with the exception of the local disease under which he has laboured, and the circumstances attending the separation of the tumour. The origin of this he describes in the following words.—"About twenty-three years ago, a little pimple, like a wart, appeared just under my left eye, close to my nose. I scratched off the head of this pimple; which formed a scab; and ever since there has been a growth from under that spot."

The tumour, although slow in its growth and free from pain, gradually increased in size, became more conspicuous, and proceeded to produce extreme disfigurement of the face. The turbinated and cellular apparatus on the left side of the nose were destroyed; the septum nasi was pushed towards the right side, so as nearly to obliterate the right nostril; and the left orbit was thrust outwards.

In a short time, the growth of the tumour displaced the inner wall of the orbit; and the globe of the eye, being then subjected to pressure, became the seat of most excruciating pain, though vision was very little impaired: the symptoms however continued; until, about seventeen years ago, the globe, yielding to the pressure, burst, and gave exit to its fluid contents. The cicatrix of the cornea is still obvious, pointing out the part of the globe which gave way.

This yielding of the globe was attended with very little

* John Hilton, F.R.S., Surgeon to Guy's Hospital, 1845 to 1871.

bleeding, but it produced almost complete relief from pain. In less than an hour, the patient, who had been deprived of rest during several weeks, was buried in profound sleep; which lasted so many hours, that his friends began to be alarmed. He awoke nearly free from pain; and this comparative ease has continued up to the present time. He has, however, been the subject of occasional neuralgic pains following the distribution of the first and second divisions of the fifth nerve.

The tumour fortunately did not extend backwards towards the pharynx or air-passages; so that the patient has never experienced any difficulty in swallowing, or breathing through his mouth; and has always been able to speak with as much distinctness and clearness of articulation as at present, his voice being now characterized by what is termed a nasal sound.

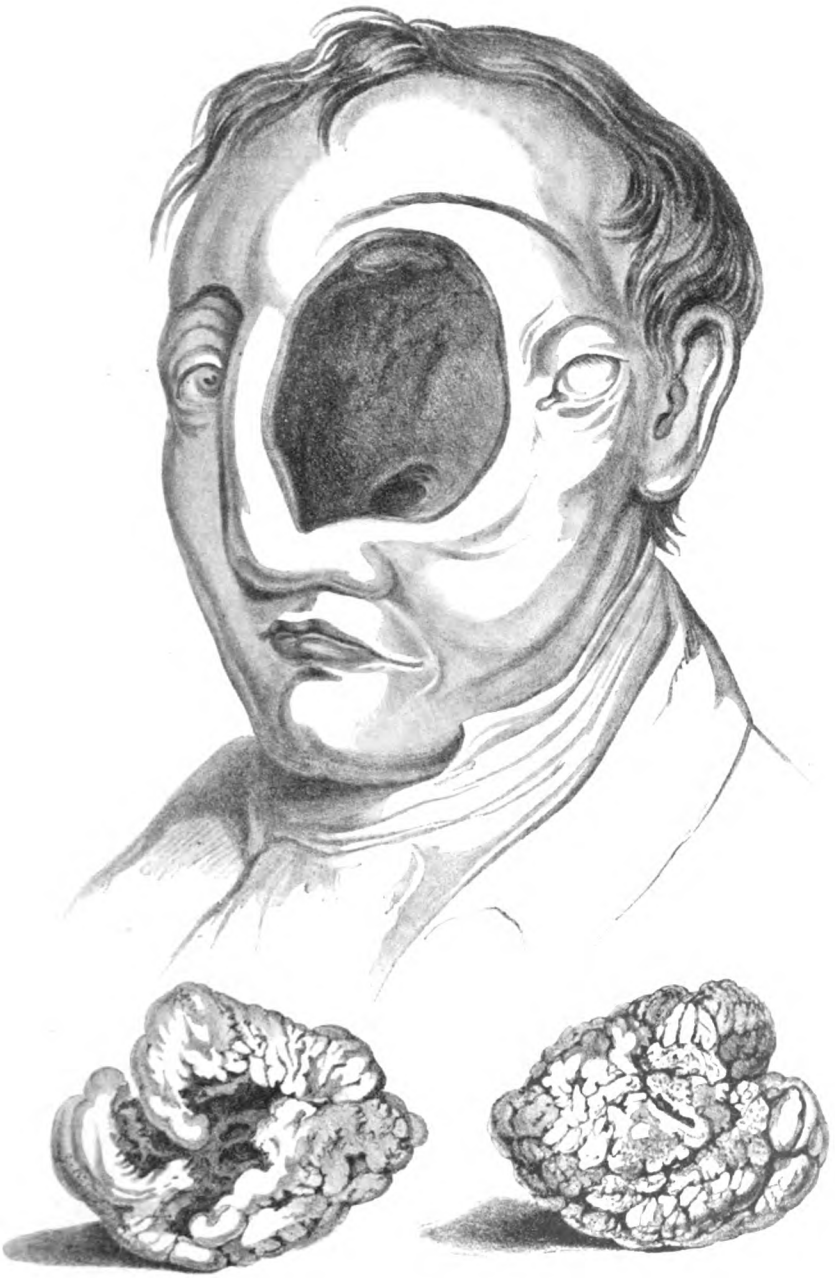
About six years ago, the tumour was observed to be somewhat loosened, and detaching itself by ulcerative absorption from the surrounding soft parts, the integuments being destroyed by its pressure forwards. This process was accompanied by copious suppuration, and occasionally by profuse arterial hæmorrhage, proceeding not from the vessels of the tumour itself, but from those of the adjacent structures about the situation of its origin, near the internal angle of the orbit.

Through the kindness of my friend, Mr. Gilson, surgeon at Chelmsford, I saw this patient about eighteen months ago. The tumour was then exposed and moveable; and retained in its situation by bands of integument, which we proposed to divide, with a view to the removal of the bony mass: but the circumstances under which the patient was placed prevented the performance of this operation.

Shortly after this time, several small irregular portions of bone came away: but the large mass, without causing pain, continued to be maintained in its situation until the transverse bands of skin were divided by ulceration; when, to the patient's great astonishment, the whole tumour fell from his face. Neither pain nor bleeding attended this separation; but a large chasm was left, which is accurately represented in the accompanying sketch. (Plate I, Fig. 1.)

It was bounded *below* by the nasal surface of the hard palate and the floor of the left antrum: *above*, by the left frontal sinus and left half of the cribriform plate of the æthmoid bone: *internally*, by the septum nasi, which presented a general concave surface, with a small opening through it, at the lower part, communicating with the right nostril; and *externally*, by the left orbit. *Posteriorly*, it opened into the pharynx.

PLATE I.



The roof, the outer wall, and part of the inner are now covered with granulations, more or less abundant, with here and there small portions of bone, denuded but not presenting any malignant character. . . .

The tumour weighs fourteen ounces and three quarters. Its density is remarkable, the specific gravity being 1·80. Its greatest circumference measures rather more than eleven inches, and its least nine inches. The external surface (Plate I, Fig. 2) is irregularly nodulated; and an uneven concavity (Plate I, Fig. 3) exists at the posterior part. A section (Plate II, Fig. 2) presents a very hard polished surface resembling ivory;

PLATE II.

and exhibiting lines, to the number of fifty, arranged in concentric curves, enlarging as they are traced from the posterior part. The formation and structure of the tumour is described in the following letter, addressed to me by Dr. Hodgkin.

" DEAR FRIEND,

" The form of the bony tumour, which thou hast been kind enough to send for my inspection, is so irregular as almost to defy description. . . .

" . . . The section exhibits a structure of great compactness, more resembling ivory than bone, but possessing, I conceive, still more nearly the character of the crusta petrosa in the molar tooth of an elephant. . . .

" The remarkable tumour . . . possesses a degree of hardness, which seems to exceed that of bone or ivory. Where not discoloured by the decomposing secretions with which it was in contact before it dropped, it is of a dead white: the surface of the section bears a high polish; and exhibits concentric

lines, conforming themselves to the circumference of the tumour. . . . One remarkable feature in this tumour is, that its attachment to the bones of the face, if it ever possessed any, was so extremely limited, that it cannot be made out in its present state;—a circumstance which may have contributed both to its ossification and separation. . . . .

" Thine truly,

" THOMAS HODGKIN."

" *Finsbury Circus,* 31, 8, 1836.

July, 1836. . . . The opening in the face, previously occupied by the tumour, now exposes, in their perfect state and natural position, the pharynx, and the hard and soft palate; and admits a view of them, as employed in simple respiration, or in those circumstances or efforts, to the due performance of which either inspiration or expiration is essential; as, for instance, in the completion and full evolution of the voice, the formation of letters, the construction of words, and also during the process of deglutition.

This rare opportunity of viewing the soft palate and pharynx engaged in their natural actions enables me to describe their modes of operation: and their condition in this case was so healthy, and their motions and adaptations so obvious, as to leave little room for doubt or disputation, and to render unnecessary any reference, on my part, to the opposing opinions of physiologists.

Respiration.—In the first place, it is to be remarked, that although the opening in the face is much more extensive than the nasal cavity in its natural condition, it must still be considered to represent, or be analogous to it, during the performance of nasal respiration.

During quiet and unconstrained breathing, *with the lips closed* so that the air must pass through the nose and opening, there is not any perceptible movement upwards of the soft palate; nor does the pharynx advance. The latter remains perfectly still; and the former, we may conclude, as it disappears in the descending direction, is closely adapted to the back part of the mouth, so as to leave, for the air passing to and from the larynx, a free and spacious canal.

When *the lips are slightly separated,* so that the respiration is in part carried on through the mouth, the soft palate is seen to be carried, or rather, perhaps, drawn upwards and backwards at each inspiration, and at each expiration again to decline; the pharynx continuing almost at rest, but having a slight disposition to advance.

Upon taking a full inspiration through the mouth, the palate is directed more completely upwards and backwards, and adapts itself to the advancing pharynx. This adaptation remains until the expiration has nearly terminated: but it should be remarked, that the sides of the pharynx do not, even in this case, approximate so much as during deglutition.

From these observations we may conclude, that during hurried or forced inspirations and expirations made with the mouth widely opened, nearly all, if not the whole of the air which enters and escapes from the pharynx and larynx is excluded from the nose, and takes its course through the mouth.

This arrangement appears suited to prevent the forced admission of air into the tympanum, through the Eustachian tubes; which would influence very materially the condition of the membrana tympani, and render it insusceptible of proper modification through the medium of the chain of bones.

It likewise serves to maintain the olfactory apparatus in an uninterrupted state of efficiency; which would doubtless be impaired, were the mucous lining of the organ of smell rendered dry, by too much exposure to the rapid transit of air. The importance of this provision is forcibly exemplified in the condition of a dog hunting by scent: for occasional inspirations only being made through the nose, the delicate sensibility of the olfactory organ is maintained.

Thus, by a simple provision, determining the direction of the air, the functions of hearing and smelling are preserved in an effective state. . . .

In whistling, which is produced by forcible expiration through the mouth, the palate is seen to ascend rather more completely than in full and easy respiration; and there is but very slight advance of the pharynx, but sufficient to compel the column of air passing from the chest to obtain its exit through the mouth. The whistle, however, can be but imperfectly effected, in consequence of some of the muscles of the lips having lost their bony attachments or fixed points; and also from the facial, their motor nerve, having been in part destroyed.

As soon as the expiration has apparently ceased, the palate descends, and the pharynx retires to its state of repose.

The same remarks apply in reference to the movements of the soft palate and pharynx, during the act of coughing; and we may infer that the air in neither case receives a direct impulse from the palate or pharynx.

In holding the breath, as it is termed, or forcibly retaining the air in the chest, either with the lips closed and the tongue

depressed; or with the tongue raised and adapted to the concave surface of the hard palate, and the lips separated; or, lastly, with the superior and posterior portion of the tongue applied, by great voluntary effort, to the concave commencement of the soft palate, the lower jaw being depressed and carrying with it the genial portions of the genio-hyo-glossi muscles; the pharynx advances, and the palate is much raised, presenting a convex surface upwards, undulating, with a somewhat tremulous motion, upon the subjacent column of air.

I may also remark, that unless, superadded to this essential condition of the palate and pharynx, some one of these adaptations takes place, namely, of the lips to each other, or of the tongue to the roof of the mouth, or of the dorsum of the tongue to the origin of the soft palate, an expiration cannot be prevented from following inspiration almost immediately; clearly showing, that the retention of the air in the chest cannot be accomplished, or, at most, can only be kept up for an exceedingly short time, by the thyro-arytenoid and arytenoid muscles bringing the inferior chordæ vocales into approximation.

The integrity of the soft palate, then, is to be considered of importance, in keeping the chest distended with air;—a condition, on certain occasions, highly advantageous, in giving stability to those points to which the origins of some of the muscles of the upper extremity are attached.

Sneezing may be described as composed of two efforts—inspiration through the mouth, followed by expiration through the nose. During this act, the whole of the air retrogrades through the upper part of the pharynx and the nose, the palate being adapted to the back of the mouth, and the pharynx tranquil: but if sneezing happens many times in quick succession, so that the palate has scarcely time after its elevation, during the oral inspiration, to descend to the back of the mouth before the air returns from the chest, the palate is then seen violently agitated by the air in its ascending direction, being at that time obliquely placed with respect to the expired air, so that a portion of the air passes through the nose, and a portion through the mouth, giving the coarse tearing sensation to the palate, and flapping motion of the lips, experienced in the imperfect attempt to sneeze. . . .

Deglutition.—When the mouth is open to receive the food, the palate is raised, but not so completely as in full oral inspirations: the sides of the pharynx also approximate, but not so closely as on drawing the breath inwards: the posterior part of the pharynx advances but slightly. Directly

the food, either solid or fluid, is placed in the mouth, the palate descends, and continues, during the detention of the food, closely adjusted to the back part of the mouth, the pharynx remaining perfectly quiet. These conditions are to be observed during the process of mastication, performed with or without food in the mouth. Extreme lateral movements of the jaw encroach upon the pharynx but very slightly; and in the ordinary lateral motion, there is no difference to be observed in its capacity. Immediately antecedent to that part of the process of deglutition occurring in the passage of the food between the fauces and pharynx, or when the food is passing backwards over the upper opening of the larynx, the palate is carried *completely* upwards and backwards, and the pharynx advances, the sides of which more especially approximate. At this time the thyroid cartilage rises. These movements of the larynx and palate occur nearly simultaneously, those of the palate having but a momentary precedence. The palate and pharynx being now nicely adjusted, their common surface presents, from above, a hollow cone, in consequence of the partial descent of the palate; but so closely is their adaptation maintained during the deglutition, that not the slightest portion of the passing substance is perceived above the palate. At that moment the pharynx is indeed divided into two distinct cavities; one at the upper part common to the nose and pharynx, the other open to all the apertures below the palate. As the fluid or food passes into the lower part of the pharynx, the upper portion recedes or retires from the palate; the soft palate falls; and, last in this succession of events, the larynx, as is indicated by the motion of the thyroid cartilage, descends.

The sensibility to pressure, as a stimulus to action, of the back part of the soft palate, and of the internal aspect of the pharynx, seems much diminished whilst mastication is proceeding; at that time, the soft palate, occupied in keeping the food in the mouth, may be touched, without inducing the disposition to swallow; but if similar pressure be exerted upon the same part when there is no food in the mouth, the process of deglutition is induced, accompanied by a sensation of tickling. The sensibility of the back part of the palate is not quite so acute as that of the anterior.

Whilst detaining *a very large and distending quantity of* fluid in the mouth, the palate is extremely raised, presenting a convex surface upwards. This state can be maintained for some time, although with difficulty and fatigue, in consequence of the extremely convex position and retraction of the tongue, which are necessary, to adapt it to the elevated

palate. Any pressure upon the back part of the palate at this time induces the pharynx to come forward involuntarily, in the same manner as it does in the process of deglutition.

Position of the palate during the formation of letters and words.—Complete utterance occurs only during expiration; and whilst repeating the alphabet, the soft palate rises at the beginning, and again descends at the termination of each letter or expiration; the sides of the pharynx, also, slightly approximate. The louder the voice, the more apparent are these actions in the palate and pharynx. The extent of this adaptation of the palate and pharynx in the ordinary voice resembles that which occurs in the mildest oral expiration; with this difference only, that the palate is rather more steady in the process of articulation or formation of the letter, than in simple expiration.

The articulation of each of the vowels, and the letter Y, produces about the same extent of elevation of the palate.

I have not had time to note and classify the relative elevations of the palate in the formation of the consonants; but, from what I did observe, it appeared that, in the formation of the letters H, M, and N, the soft palate is employed actively, and especially so in the letter M. . . .

Reverting to the position of the palate in its quiescent state, it may be described as presenting an anterior concave surface, facing downwards and forwards; a posterior convex surface, facing upwards and backwards; an anterior attached edge; and posterior free or uvular edge.

The closest adaptations between the palate and pharynx seem to occur in the attempts to retain the air in the chest and pharynx, and during deglutition. In the former case, the excess of effort appears in the palate: in the latter, the chief action devolves upon the pharynx.

During these close adaptations, the posterior or uvular edge of the palate has a direction towards the pharynx, each side of which presents a convex surface, probably produced by the contractions of the petrous origins of the superior constrictor. These convex surfaces look inwards and forwards; and fit into the concave edges of the soft palate, between the uvula and pillars of the fauces. The uvula itself is received into the hollow created in the middle of the posterior surface of the pharynx, in consequence of that middle or occipital portion being more fixed; which may be partly attributed to the strong cellular attachment of the superior and middle constrictors to the anterior aspects of the first and second cervical vertebræ.

OBSERVATIONS ON THE EXCRETION OF URINE IN A CASE OF ECTOPIA VESICÆ

By L. S. DEBENHAM, M.B.; J. JOFFE, M.B., and M. S. PEMBREY, M.D., F.R.S., Professor of Physiology. (From the Physiological Department, Guy's Hospital.)

INTRODUCTION

THE presence in the wards of a patient suffering from complete ectopia of the bladder afforded an opportunity of observing the influence of certain factors upon the excretion of urine, especially the relationship between the activities of the skin and the kidneys.

CLINICAL DESCRIPTION (by Alan Todd, M.S.)

William B., aged seven years, was admitted to Naaman Ward, under the care of Mr. L. A. Dunn, on September 21, 1915. Apart from his malformation he was well-grown, active and healthy. There was complete epispadias and external examination revealed no testes. The posterior wall of the bladder, with the trigone, was exposed on the surface of the abdomen. The mucous membrane was thick and bright red, and the skin around was not excoriated, although just about the vesical margin it was rather sensitive to touch. The orifices of the ureters were normal, appearing as two oblique valvular slits, and showed no tendency to prolapse. The vesical mucous membrane bulged forwards and on gentle palpation it was found that there was a firm, smooth and bilobular lump behind it; this, there is little doubt, was the prostate. A few punctate depressions close to the ureteric orifices marked the site of the openings of the prostatic and ejaculatory ducts. The corpus spongiosum was represented by a turgid, vascular mass of tissue lying ventral to the trigone; it was quite rudimentary. This was all that existed to represent the genital folds of the fœtus; the parts normally derived from the genital tubercle and the genital swellings were entirely suppressed. The pubic symphysis was cleft, the separation amounting to about one inch, and the two surfaces of the pubic bones which are normally in coaptation were everted to such an extent that they looked almost directly upwards. The pubic spines, therefore, were a considerable distance apart. The posterior superior iliac spines were correspondingly nearer together than usual. The effect

of the cleft in the pelvic girdle was to render the gait unstable, and the child walked in a shaky way which was characteristic. He was prone to become tired if he ran about for long, but he stood or sat up a great deal, for he had learnt apparently by experience that he never felt so well if he lay down much. Presumably this means that the drainage from his urinary tract was better when he was in the erect posture. The ureteric orifices were of normal size, but it was noticed during catheterisation that the ureters above were slightly dilated. The kidneys were examined by palpation and by the x-rays, but no evidence of abnormality was found. There was no clinical evidence of chronic uræmia. The child suffered from nothing beyond the inconvenience of his deformity. He wore a rubber urinal by day and this sufficed to collect the urine without leakage. The vesical mucosa was generally not hypersensitive; indeed, it appeared to be less sensitive than one would have expected; this was due probably to anaplasia. In a similar case in which the mucosa was examined microscopically it was found that it had undergone a change from the transitional to an ordinary stratified squamous type, the cells on the surface being definitely keratinised; but a part which had been covered over by a plastic operation in earlier years retained its usual histological characteristics and ordinary sensitiveness. In the present case, however, no such operation had been performed, and it is probable that the whole of the mucosa that was exposed had undergone anaplasia. It was noticed that whenever he got a little cystitis, as, for instance, after being in bed for several days, or receiving less water than he desired, his vesical mucosa became very red, congested and sensitive.

Excretion of Urine: Relationship between the Activities of the Skin and the Kidneys

The observations were made after the patient's midday meal, for as a rule he fell asleep immediately after the meal, and no difficulty was experienced then in retaining, without any leakage, the cannulæ in the ureters. There was also the advantage of avoiding any psychical effects, which might cause variations in the rate of the urinary excretion.

In the first observation the boy slept with the skin of the body exposed to the air of the ward for two hours, and the rate of the excretion by each kidney was determined. The activity of the skin was then increased by the application of warm blankets and hot-water bottles; the patient was awakened and drank one half-pint of hot weak tea. He then fell asleep,

and as soon as sweating was definitely established the measurement of the rate of the flow of urine was continued. It may be objected that the diuretic effect of the tea would vitiate to some extent the observation; this diuretic action, however,

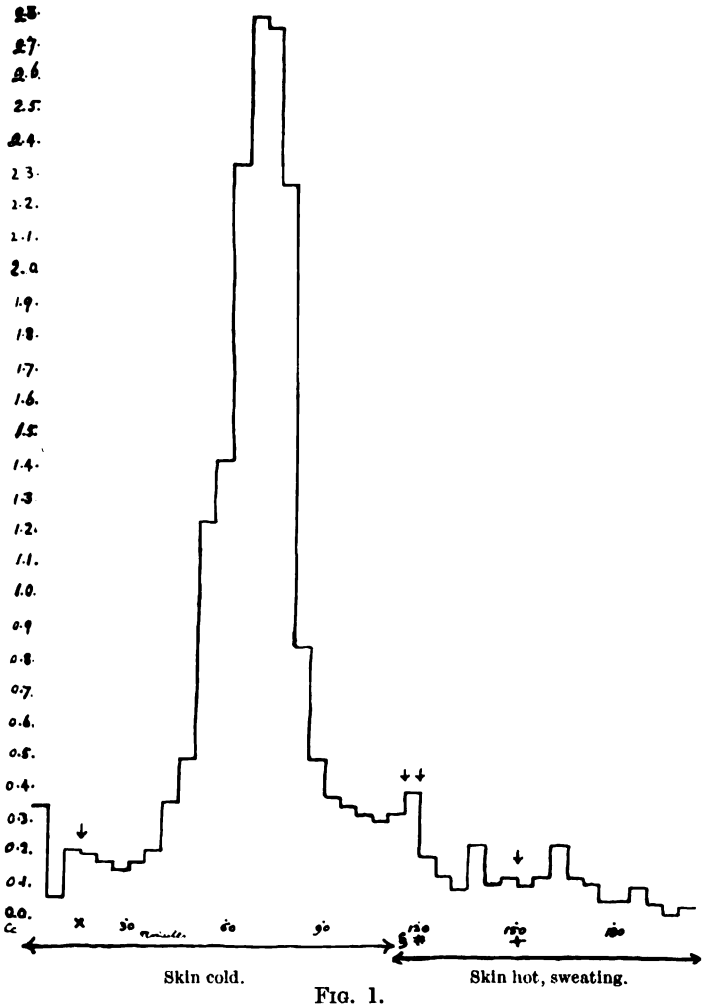


FIG. 1.

Outflow of urine from left kidney. Volume in c.c. per minute. Duration of observation shown in minutes. Skin at first exposed, cold. ↓× half a pint of water given with the mid-day meal; skin covered with warm blankets ↓ §, and warm-water bottles applied ↓ ‡‡; half a pint of hot tea given at ↓ +.

appeared to be more than compensated by the increased quantity of blood present in the skin during the second period of the observation.

In the second observation made on the same day the conditions were reversed. The skin was kept warm, but not hot

enough to cause sweating, for about one hour and a half; then the patient was awakened and given half a pint of warm tea. The bed-clothes were entirely removed and the skin was in this way cooled. The results of these two observations are most readily given in a graphic form (Figs. 1, 2 and 3).

The curves show in a striking manner the reciprocal effect of the blood supply in relation to the skin and the kidneys; when the skin was cold, pale and dry the diuretic effect of the tea was demonstrated by the rapid output of urine. When, on the other hand, the skin was hot, flushed and wet with sweat, the kidneys remained inactive. A feature in both curves is the

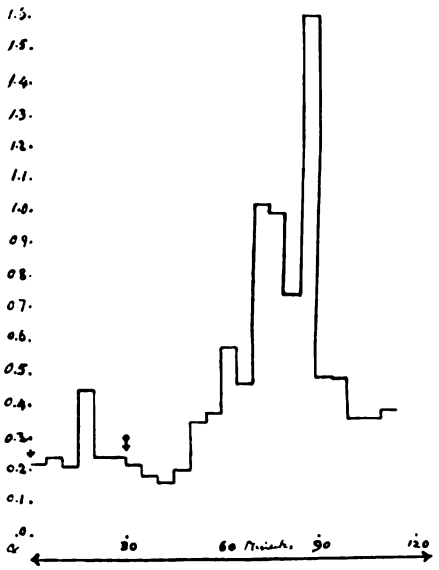


FIG. 2.

Outflow of urine from left kidney. Volume in c.c. per minute. Duration of observation shown in minutes. Skin cooled by exposure at ↓; half a pint of tea given at ⇓.

decrease in the rate of the excretion of urine, which precedes the rise, caused in the one case by one half-pint of warm tea and in the other by an equal amount of hot tea. We suggest that this decrease may be due to the withdrawal of blood from the kidneys to the intestines for the purpose of absorbing the fluid. The rapidity with which fluids are absorbed from the bowel would explain the short duration of this diminished output of urine. In the first observation it will be noticed that there is a much less definite decrease in the urinary flow when the hot tea was taken during the stage of sweating. The results charted for the right kidney lead to similar conclusions.

The Comparative Activity of the Two Kidneys

It was found that as regards the volume excreted per minute and the composition of the urine the right and left kidneys were not identical. Careful attention to the prevention of leakage around the cannulæ showed that this difference was real and not due to experimental error; so too did estimations repeated on different days. There was one difficulty to consider; at times there might be a gush of urine from the one or the other ureter, but these occasional gushes were insufficient

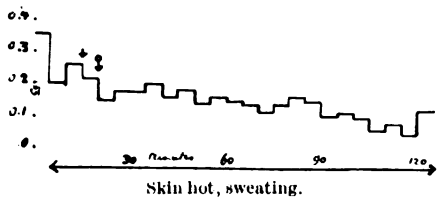


Fig. 3.

Outflow of urine from left kidney. Volume in c.c. per minute. Duration of observation shown in minutes. Skin hot and sweating. Hot-water bottles applied at ↓ and half a pint of water given at ↓.

to affect the general conclusions drawn from observations extending over some hours. We thought that this difference in the two kidneys might be due to disease, but this view we abandoned, because we found on repeating our observations that the concentrations of the urines from the right and left kidneys respectively varied in different directions on different days. Thus on October 8 the right kidney excreted a less concentrated urine than did the left in respect to both chlorides and nitrogen (hypobromite method).

	Right.	Left.
100 c.c. urine during control . . .	64·5	73·5 c.c. $N/10$,$AgNO$
„ „ „ control . . .	830	920 c.c. moist N
„ „ „ diuresis . . .	20	32 c.c. $N/10$,$AgNO_3$

If either kidney were diseased, a lower concentration in both chlorides and nitrogen would be expected. The figures above represent about 2·3 per cent. and 2·5 per cent. of urea and over 0·2 per cent. of chloride, values within normal variations.

On October 10 the urines from the right and the left kidneys were more equal, but the right was excreting a more concentrated urine, both as regards total solids and chlorides.

	Right.	Left.
100 c.c. urine during control . . .	96	89 c.c. $N/10$,$AgNO_3$
„ „ „ control . . .	3·6	6·0 grms. total solids

We were unable at any time to find albumin, casts, blood or any abnormality indicating renal disease. The urines always

showed a slight haze, which cleared up on filtration; this appeared to be due to desquamation of cells of the mucous membrane of the lower end of the ureters.

The following table of volumes of urine passed every five minutes shows that there was apparently no definite ratio between the two kidneys, both before and during diuresis.

Right:	0·7,	0·8,	0·7,	0·6,	0·5,	0·6,	0·6 c.c.		
Left:	0·9,	0·7,	0·8,	0·75,	0·65,	0·7,	0·8 c.c.		
Right:	4·9,	4·5,	8·0,	4·0,	6·7,	6·8,	10·0,	12·0 —	5·2 c.c.
Left:	1·0,	1·75,	1·85,	2·9,	2·3,	5·6,	4·9,	3·7,	8·2, 2·4 c.c.

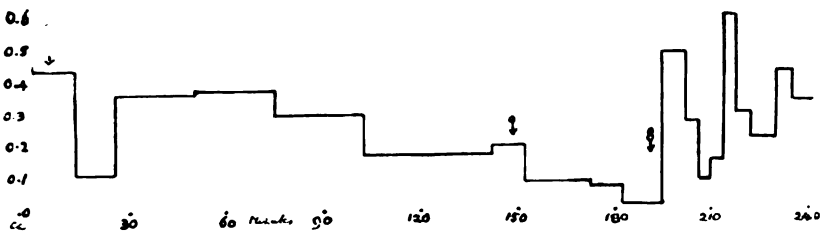


FIG. 4.

Outflow of urine from left kidney. Volume in c.c. per minute. Duration of observation shown in minutes. Half a pint of water given at ↓; subcutaneous injection of pituitrin at ↓, and half a pint of tea given at ↓.

We made a further attempt to compare the excretory powers of the two kidneys by means of methylene blue. Four grains of the drug were given as a pill with the midday meal, but no definite coloration of either urine occurred, although the observations were continued for five hours. The urine developed a faint blue colour on being kept in a cold room for twenty-four hours, but it was too feeble for colorimetric determinations.

EFFECT OF PITUITRIN

An attempt was made to produce diuresis by subcutaneous injection of pituitrin. A dose of 0·75 c.c. of the drug was injected while the patient was asleep. He awoke, and his systolic brachial blood pressure rose from 83 to 95 mm. Hg. This rise was maintained for so short a time, less than fifteen minutes, that it is impossible to maintain that it was due to the pituitrin and not to the psychical effect of the injection. No diuretic effect could be found. It has been suggested that the failure to provoke diuresis was due to the commercial origin of the preparation, but it is of interest to note that Kennaway has found that subcutaneous injection of pituitrin in healthy adults is followed by a decrease in the output of urine; moreover, successful results have been obtained by the treatment of the polyuria of diabetes insipidus with this drug.

THE COLOUR-INDEX IN ADDISON'S ANÆMIA
A COMMENTARY ON J. M. H. CAMPBELL; AND J. J. CONYBEARE'S PAPER ON ADDISON'S ANÆMIA [1]

By GORDON W. GOODHART, M.B., Clinical Pathologist, University College Hospital, late Douglas Demonstrator of Pathology, Guy's Hospital.

In their paper on Addison's anæmia in the July 1922 number of the Reports J. M. H. Campbell and J. J. Conybeare make some very interesting observations on the colour-index. Amongst their conclusions they say that a colour-index of between 0·7 and unity is almost as common as one between unity and 1·2, and quite as common as one between 1·3 and 1·6. This might possibly be true, though I do not think it is, without upsetting my own belief that a colour-index of less than 0·8 practically never occurs in this disease; but it is clear from the tabulated details as well as from the general tenor of their paper that they consider a low colour-index need not necessarily cause any hesitation in coming to a diagnosis of Addison's anæmia. This is so directly contrary to my own experience that I have collected my records of all the cases that have been diagnosed as pernicious anæmia at University College Hospital during the period that I have been in charge of the clinical laboratory, *i.e.* from July 1919 to August 1922. These cases number twenty-four, and amongst them there is only one in which a colour-index of less than 0·85 was ever observed; in this case the colour-index during a period of eight weeks' observation was never found to be as high as 0·6, the mean diameter of the cells was diminished, and there was a relative increase in the polymorphonuclear leucocytes in the differential count; on Campbell and Conybeare's own showing this case was presumably not one of Addison's anæmia. If we exclude this case we are left with twenty-three cases and a total of seventy counts without one colour-index lower than 0·85. Tabulating them according to the colour-index they are as follows :—

Colour-index	Under 0·8	0·8–0·9	0·9–1·0	1·0–1·2	1·3–1·5	1·6–2·0
Number	0	2	7	43	15	3
Percentage	—	3	10	61	22	4

In both the cases which gave one count with a colour-index of 0·85 the red cells had risen to over four million per c.mm.

This collection of cases would be much too small to put up against the Guy's series, but for the fact that the conclusion as to the rarity of a low colour-index which it supports is the one which is theoretically probable in consideration of the known facts. That Addison's anæmia is characterised by the large size of the red cells has been generally admitted for a long time, and that this is the essential feature of the disease has now been conclusively proved by Price Jones,[2] whose recent work on this aspect I look upon as the greatest advance in establishing the pathological entity of the disease that has been made for many years. Moreover, a frequently occurring low colour-index seems quite incompatible with Campbell's[3] own conclusions as the result of his very interesting work on the volume-index; and the same may be said of the work of Capps[4] and Gram,[5] although, as I am by no means enamoured of the technical methods employed here, I lay no undue stress upon it.

In searching for a cause of the discrepancy between my statistics and those of the Guy's series we come at once to the crucial question of the reliability of the figures. With regard to my own figures, the counts were with very rare exceptions done by myself, and even the exceptions were carefully supervised and checked by me; the apparent conceit of my own counts underlying this remark I hope to minimise a little later. On turning to Campbell and Conybeare's paper I find little in the way of internal evidence on this point; but there is the statement that the counts have been done not only by ward clerks, but also by experts whose reliability will be generally admitted; from this I assume, perhaps wrongly, that the majority have been done by ward clerks. There is also the statement that the agreement between their figures and those of French's earlier series is sufficiently close to show that the figures are accurate. Here I am entirely at issue with the authors, for I look upon this agreement with great suspicion. In French's paper the details of all the counts are given, and reference to it gives, I think, conclusive proof of inaccuracy in the counts. For instance, the performance of the marrow in Case 28, where the red cells jump from $1\frac{1}{2}$ to $4\frac{1}{4}$ millions per c.mm. in five days, is reminiscent of the story of the loaves and fishes on the shore of Lake Tiberias. Case 18 shows a very suspicious and sudden change in the blood picture in October, a date that is coincident with a change in the medical ward clerks; and Case 45 also shows counts that I can hardly believe are all of them right. Of this last case I speak without bias and with some authority, as

I believe that I was the clerk responsible for the December counts, and only the other day I threw away some faded relics of the past in the shape of blood films from this case. These are more or less extreme examples, but throughout the series there are in individual cases variations in the estimation of red cells and hæmoglobin, which in their rapidity and degree are quite outside my experience. French, indeed, emphasises the variations in the colour-index as a feature of the disease, and to this within limits I agree; the details given in his paper are widely beyond those limits.

Further, in considering French's figures no one who remembers the methods adopted by the ward clerks and the conditions that obtained in those days, and who is at the same time familiar with the scrupulous attention that must be paid to the minutiæ of technique, if reasonable accuracy is to be obtained in making blood counts, can possibly maintain that the figures of the earlier series are likely to be of that order of accuracy that is essential if they are to be used as a basis for a statistical study. I am not aware how much change there has been in this respect since 1918, but this criticism of the reliability of French's figures will, I think, hold good for most of the routine counts in the later series that fall before that year.

I therefore believe that the frequency of a low colour-index in the Guy's series may be explained by inaccuracy in the blood counts. Campbell has himself investigated with great care a small series in his observations on the volume-index, and it would be very interesting to know whether any counts in this series show a colour-index of less than 0·8.

With regard to the stress I lay on the accuracy of my own counts, I would like to make it clear that this is not based on the mere fact that I made the counts myself. I would by no means claim equal weight for the many counts I have made, say, in the routine examination of a long series of cases of heart disease; these have been, I hope, of sufficient accuracy to establish the presence or absence of an anæmia and to gauge its progress, but I make no claim that they form a suitable basis for any statistical study. On the other hand, the cases of Addison's anæmia have all been investigated with the definite purpose of getting figures as accurate as is possible with our present methods, and scrupulous care has been taken over all of them. I hope that this will make it clear that I am not criticising the practice by which blood examinations are made as a matter of routine by ward clerks. I believe this practice to be most desirable, and I hope that it may long flourish at Guy's; but it does necessitate certain sacrifices, and one of

these is the ability to base statistical conclusions upon them.

It may, of course, be that further experience will bring me cases with a low colour-index, but I cannot help feeling that, if such cases were really as common as the Guy's figures suggest, some at least would have occurred in my series by now. In practice the point is probably of small importance, and I should not have ventured to elaborate it so extensively anywhere but in a Guy's journal; but in the traditional home of our knowledge of Addison's anæmia I may perhaps be allowed a greater degree of licence than would otherwise be permitted.

I hope that it will not be thought from these remarks on French's figures that I wish in any way to belittle the general value of his paper; on the contrary, that paper is still my trusted guide, with all its wealth of clinical observations, and I am in particular grateful for the laborious detail with which the blood counts are recorded. But it was written more than twelve years ago, and I hope that we have in that time made some advance in our realisation of the many pitfalls there are in routine blood examinations. If so, there is no irreverence in reviewing old figures in the light of wider knowledge.

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FURTHER NOTE ON THE COLOUR-INDEX IN ADDISON'S ANÆMIA

By J. M. H. CAMPBELL, M.D., and J. J. CONYBEARE, M.B.

WITH Dr. Goodhart's general comments we are in almost complete agreement, but one or two additions may make some apparent discrepancies more easy to understand.

The blood counts on which our figures are based are those given in the reports. About one-third of these were done by hæmatologists, about one-third by the clinicals, and the remainder by the ward clerks. In the latter cases counts have been excluded, if there were obvious disagreements over a short period of time, so that the figures given generally represent two or more concordant blood counts.

We agree that the figures are not entirely accurate owing to personal errors and to the different instruments used, but we think that the figures quoted are valuable in helping to decide for or against a diagnosis of Addison's anæmia.

We do not agree that the general tenor of our paper was that a low colour-index need not cause any hesitation in coming to a diagnosis of Addison's anæmia. We stated that "many healthy persons have a colour-index of 0·9 or 0·8, and, if this be accepted, a subnormal colour-index is rare in Addison's anæmia." This figure is almost the same as the lowest figure found by Goodhart in his cases, and our personal experience agrees with this.

This colour-index below unity in normal persons means that the average size of the red cells may be increased while the colour-index is still not greater than unity.

Our reason for mentioning the figure 0·6 in the summary was that we wanted to be able to make a definite statement that the colour-index was *never* below 0·6, and to this there was only one exception. We are now very doubtful about this one exception. The blood count with a colour-index of 0·5 was apparently reliable, but in a long and careful series of subsequent counts it has never been below 0·9, so that we think there must have been some error. The full figures given in the Appendix and in the figure show how relatively rare are colour-indices under 0·8, but we were anxious not to overstate the case by saying that the colour-index was *never* under 0·8. In the very short series of cases carefully examined by one of us the colour-index was never under 0·96, but these were selected cases, as the object was to study the volume of the red cells in typical Addison's Anæmia. Price Jones's most recent paper on the size of the red cells had not appeared when we wrote our paper, but we quite agree with the extreme value of his findings, especially in the analysis of the groups of cells of different sizes.

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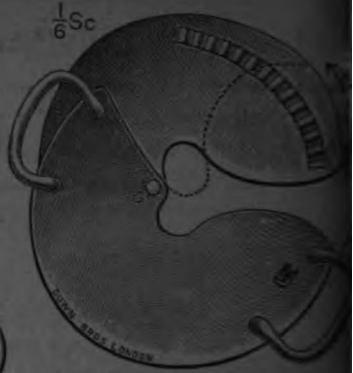

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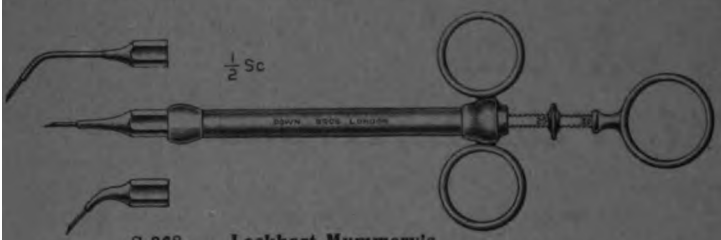

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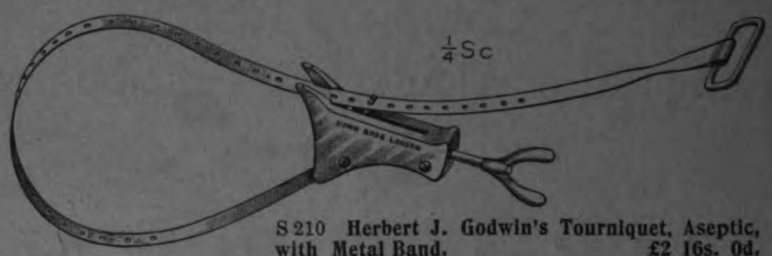

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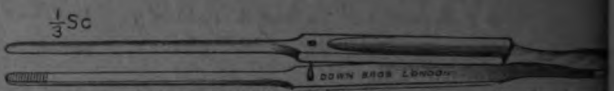

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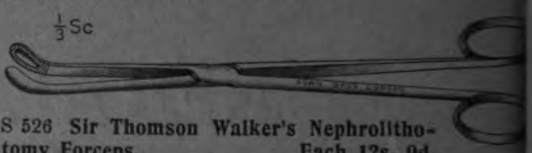

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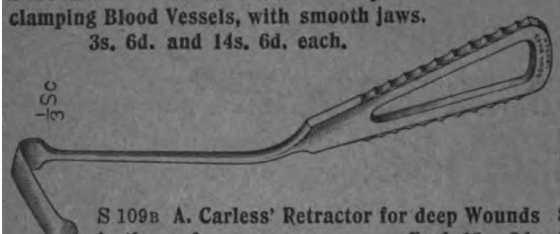

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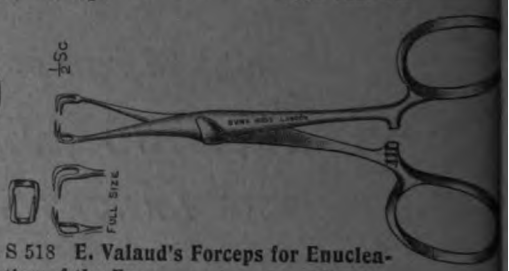

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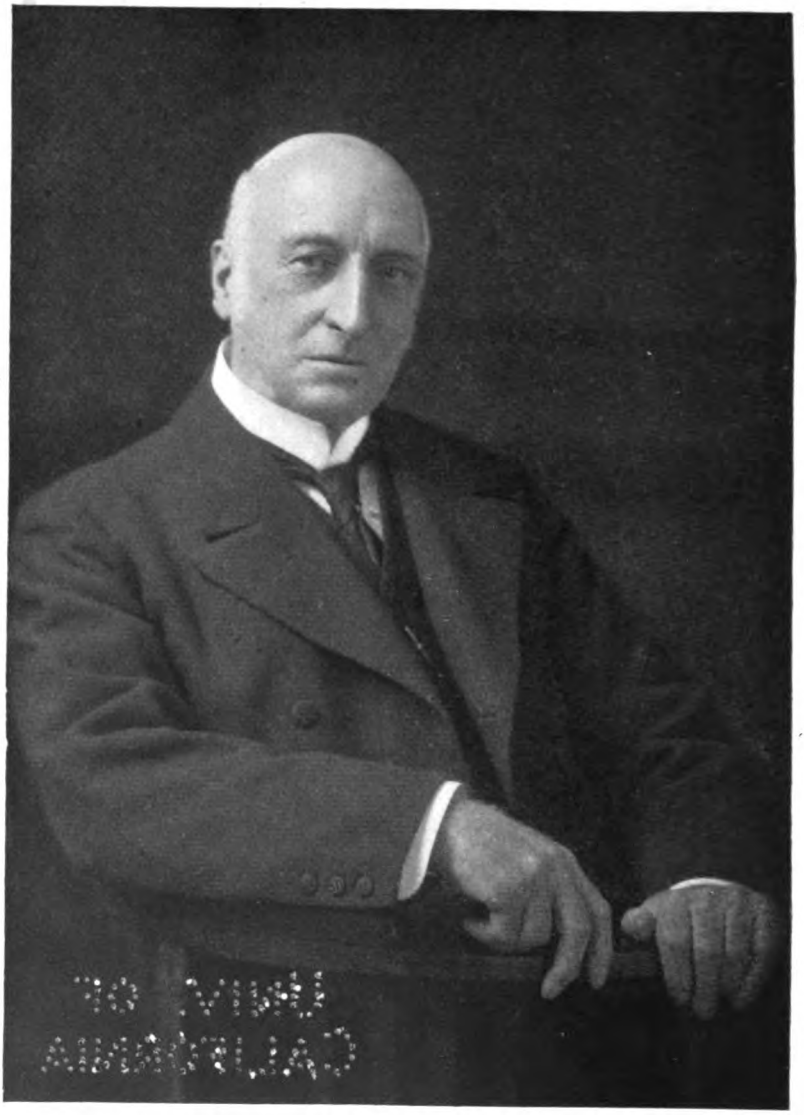

Yours very truly
Frederick W. Taylor.

SIR FREDERICK TAYLOR, BART., M.D.

By SIR CHARTERS SYMONDS, K.B.E., M.S., Consulting Surgeon to Guy's Hospital.

ANYONE occupying the position held by the subject of this memoir is called upon to play many parts: most important the faithful discharge of his obligations to the Hospital in the care of the sick committed to his charge, which will absorb the greater share of his time and energy; next his part as a teacher in the medical school and his share in its administration. Outside these immediate obligations he is called upon as a consultant to advise others in the diagnosis and treatment of the maladies of their patients; and if he take a wide view of his opportunities, to give to the profession the results of his own investigations. In this last pursuit his work redounds to the credit of his Hospital and School, while at the same time, if done in a scientific spirit, it enhances the esteem in which he is held.

How far Sir Frederick Taylor fulfilled these many duties and the position he secured in contemporary medicine, it is the object of this brief summary of a long, busy, and honourable career to relate.

Frederick Taylor was born in 1847, the son of David Taylor, a general practitioner in Kennington. His brother Herbert went to St. Bartholomew's and succeeded his father in the family practice; another brother entered the India Civil Service and perished in the destructive landslide at Naini Tal. His father was one of the old style of practitioners, a man of distinguished bearing and given to hospitality. His mother carried into her old age a charm and attractiveness which drew others towards her for guidance and sympathy. When together, one's attention could not but be arrested by the distinguished appearance of this fine old couple.

Frederick was educated at Epsom, and, having matriculated at the London University, entered Guy's in 1863 in his sixteenth year. As he used to say himself, he came to Guy's in a short jacket. At the first M.B. he gained the gold medal in anatomy and in organic chemistry, and at the final in 1868 the scholarship in midwifery and in forensic medicine and honours in medicine.

Two years later he took the M.D., qualifying for the gold

medal which was awarded to W. R. (afterwards Sir William) Gowers. In the same year he was appointed a demonstrator of anatomy, Howse being senior and B. N. Dalton his other colleague. Two years later he was appointed medical registrar, a position he held for four years. Continuing to hold this appointment, he was elected Assistant Physician to the Hospital in 1873 on the retirement of Owen Rees, his position at the early age of twenty-six being thus assured. He joined a staff of notable physicians, Habershon, Wilks, Pavy, Moxon, Fagge and Pye-Smith, while on the surgical side were Birkett, Cooper Forster, Thomas Bryant, Durham, Howse and Davies-Colley; Braxton-Hicks and Phillips were in the Obstetric Department, with Bader and Higgins Ophthalmic Surgeons.

The business of the medical school had outgrown the capacities of the old apothecary, Mr. Stocker, and required reorganising. Taylor's capacity for administration had already been recognised, and in 1874 he was appointed the first Dean, a position he held with conspicuous success for fourteen years. He laid down the lines so well and with such foresight, that further developments were easily carried out under his successors. Everything running smoothly, no one seemed to think that the work of the Dean had increased enormously owing to the many changes in the curriculum. Yet no word of protest was ever heard from Taylor, though he recognised that the demand seriously interfered with professional work. At the conference of the deans of the medical schools, Taylor's keen insight proved of signal value in adjusting the many changes in the curriculum and in bringing about co-operation.

The duties occupied a great part of his time, the preparation for the School meetings and committees absorbing many evenings, but nothing was left undone. He often felt that the clerical work entailed by the position in these days occupied the time he would rather have devoted to collating his clinical experience and contributing to medical literature. For some seven years during this period he lectured on hygiene, and when Fagge relinquished the Dermatological out-patients, Taylor for a time took charge of this department and gave lectures on the subject.

In 1874 he became associated with Howse as co-editor of the *Guy's Hospital Reports*, a position he held for ten years.

To appreciate his activities and the immense work he was doing for the Medical School, it may be said that, in the year 1875, besides being Assistant Physician with the care both of out-patients and in-patients, he was also Medical Registrar, Dean of the Medical School, Lecturer on Hygiene

and Dermatology, and co-editor of the *Reports*. Living in St. Thomas's Street, he spent nearly the whole of his time in the Hospital. From 1882 to 1885 he lectured on Materia Medica, and in the latter year was promoted to the full staff on the resignation of Sir Samuel Wilks. Within five years, owing to the untimely deaths of Moxon and Fagge, he became Senior Physician, a position he held till his retirement in 1907 on reaching the age of sixty, when he was appointed to the consulting staff. In addition to his appointments at Guy's, Taylor was for many years physician to the Evelina Hospital for Sick Children, and his position in this branch of medicine was recognised in the Presidency of the Section for Diseases of Children at the meeting of the British Medical Association held at Ipswich in 1892. He was on the staff of the Seamen's Hospital at Greenwich, while the National Hospital for Diseases of the Heart at one time secured his services, and he was also physician to several charitable institutions. He was President of the Metropolitan Counties Branch of the British Medical Association, and during the war a member of the Central Medical War Committee. In the work of this last-named Committee he took a keen interest so long as his health permitted. He served on the Commission which inspected the Hospitals in France. For many years he was a member of the Council of Epsom College—his old school—and Chairman of the School Committee.

In addition to his other activities Taylor took a special interest in the work of Convocation of his University and was associated with Pye-Smith, Cozens-Hardy and others in the effort to bring about a much-desired change in its organisation. He represented the University on the General Medical Council, and was for some time a member of the Senate. He promoted the understanding to bring together the various faculties in friendly association, and was a member of the dining club as long as it existed.

He was a constant attendant at the meetings of the Pathological and Clinical Societies, and of the Medico-Chirurgical, to all of which he made valuable communications. He was President of the old Clinical Society, the Medical Section of the Royal Society of Medicine, and later of that Society itself.

At the Royal College of Physicians he was elected a Fellow in 1879, delivered the Lumleian Lectures on " Disorders of the Spleen " in 1904, the Harveian Oration on " Medicine and Research " in 1907, and in the second year of the war was elected to the Presidency, thus attaining the highest honour in his profession. The baronetcy followed in 1917.

At different times he examined for the Universities of Cambridge, Belfast, Durham and Birmingham, and for his own University, as well as for the College of Physicians at the Conjoint Board.

The foregoing is a brief summary of Taylor's many activities, and it is only by filling in the spaces that it is possible to comprehend the enormous amount of work he accomplished. To this must be added his private practice, which, though never so extensive as his knowledge and experience deserved, was yet at one time sufficient to keep him busy. Those who knew the value of his opinion, and cared nothing for embroidery or mannerism were never disappointed.

Contributions to Medical Literature

It would be presumptuous in a surgeon to attempt to assess the value of Taylor's communications to contemporary medicine, for this would involve an intimate acquaintance with the literature of the times. I would, however, venture to express the opinion, that the articles on malignant endocarditis, on Addison's anæmia and on various diseases of the nervous system and the spleen, contain many new observations. It has been remarked by more than one well qualified to pass judgment, that the section on the nervous system in his *Practice of Medicine* was not only the best in the book, but was, moreover, the best written at the time.

The paper in the *Guy's Reports* for 1877 in collaboration with Goodhart on "The Nervous System in Diabetes," which was a reply to Dr. Dickinson, involved a great deal of labour. In this paper he showed that Dickinson's conclusions, which had, as I can remember, attracted a great deal of attention, were based on mistaken interpretations of microscopical appearances. In one particular preparation Taylor detected that the appearances described as pathological were produced by two overlapping sections, both of normal spinal cord. The paper concludes with the statement "that the pathological state of the nerve centres in diabetes cannot as yet be considered to be proved."

His contribution to the "History of Idiopathic or Pernicious Anæmia" in the *Guy's Reports* for 1878 is of permanent value, and was appropriately contributed to a publication so closely associated with the earliest descriptions of this disease. He shows clearly that the discovery of a new disease, as claimed by the Swiss observer Biermer in 1868, had been anticipated by Addison in 1853.

Space will not permit—had I indeed the requisite knowledge —a review of the many contributions Taylor made to the Medical Societies. Suffice to say that in all there was something of real value, for he was not one to write merely for the sake of publishing.

As an example of his critical handling of a subject, an extract from a post-graduate lecture delivered at the London School of Clinical Medicine (Seamen's Hospital) and published in the *British Medical Journal*, October 10, 1908, will provide a typical instance. The subject is the " Varieties of Malignant Endocarditis." He is discussing the question of classification, and after criticising the generally accepted division into the typhoid, pyæmic, septic, cardiac and cerebral groups, and pointing out how unsatisfactory is the attempt, he thus concludes this part of the subject :—

" Hence we see how difficult is the problem of classification. Classification is an artifice, almost a trick. Nature does not classify; she produces almost continuous series. Man classifies as a feeble arrangement, in order to bring within the scope of his intellect or the power of his memory the innumerable variety of facts that exist. In order to classify one must know, and the more one knows the more impossible it is to separate the numerous things from one another into distinct groups. This is increasingly obvious in any department of medicine or bacteriology. And it is true of malignant endocarditis."

The subject of the lecture was one in which Taylor took much interest, as shown by the paper in the *Guy's Hospital Reports* for 1891. This was founded upon fifty-four cases, all of which are recorded, and it affords an excellent example of his style. It contains an interesting reference to nomenclature, and the examination of the question is again quite typical of the man. While adopting the term " malignant endocarditis " as the one " most extensively adopted " he must have his parting shot, because he adds, " I feel it is not entirely good." He goes on to say that " in the case of tumours, malignant means persistent and rapid growth, recurrence after removal, reappearance in other parts of the body, and a fatal tendency. In respect of only two of these characteristics is endocarditis malignant; it persists unaffected by treatment, and it has a fatal tendency. But nobody can remove it with the knife, and in respect of reappearance the endocarditis cannot develop in remote organs." Much of this is irrelevant, for by the term malignant is meant something characterised by extreme virulence, and so we speak of malignant smallpox, cholera, etc. But Taylor loved the

meticulous, and the above is a good example of an excursion in this direction. When, however, we pass to the main subject of the paper, as with the later résumé of 1908, we find a careful, full and illuminating study of the disease.

His "Practice of Medicine"

The publication by which he is best known is the *Practice of Medicine*, a work which had a foremost place as a text-book for close on thirty years.

In the preface to the original edition Taylor states the limitations he set himself as follows :—

"I have not, however, devoted much space to the discussion of theories, finding that the facts of medicine are amply sufficient to fill, and more than fill, a volume such as this, and being convinced that these facts require to be seized and held fast by the beginners in medicine, not only for the sake of diagnosis and treatment, but also for the right estimation of the various theories which are advanced. With a brief statement, therefore, of such views I have in most cases been content."

It fell out, that in the afternoon of the day on which Taylor signed the agreement with Messrs. Churchill to write a text-book on Medicine, he joined Goodhart and myself in a river excursion. We were delighted, for such a book was needed, and we felt certain that, being written by a teacher of experience, who well knew what such a book should contain and who possessed so well-balanced a mind, prominence would be given to essentials, while other subjects in due proportion would receive attention; and, quite as important, that it would be free from any ambiguous statement. Fully aware of his love of minute analysis, with its tendency to confuse, we knew from his published papers that, when committed to writing, his views would be free from uncertainty and clearly expressed; and so it proved. The manuscript was sent to the publishers in 1889, on the day, I believe, on which his elder son was born. When published the following year, it met with instant success, some three thousand copies being sold within nine months. Needless to say he was much gratified, the pleasure being shared by his devoted wife, to whose encouragement he owed much. I recall her look of pride on showing me the pen her husband had used through these months of labour. For just upon thirty years the *Practice of Medicine* held a foremost place, its only rival being that written by Sir William Osler, the first edition of which appeared in 1892. With painstaking care Taylor revised the eleventh edition, which appeared in 1918.

This was his last effort, for it was in this year that the illness began from which he never recovered. The book to which he had devoted so much time and thought must give place to others, or, as has happened, must be edited by another. The twelfth edition published last year has been very ably edited by Dr. E. P. Poulton, who, while revising the whole work, and rewriting many parts in order to bring it up to date, points out in the preface that "the range of medicine has increased so much of late, that it is almost beyond the powers of a single individual to cover the whole ground himself. Sir Frederick Taylor and Sir William Osler will perhaps have been the last to have made the attempt." The editor has sought the co-operation of two of his junior colleagues, the one—Dr. C. P. Symonds—dealing with Diseases of the Nervous System, the other—Dr. H. W. Barber—with Diseases of the Skin. The main scope of the book remains unchanged, and so retains the impress of the author. Though the twelfth edition can hardly be expected to attain such a position as did Taylor's original publication, yet, retaining as it does the chief features of the edition of 1918, and preserving the character of Taylor's *Medicine*, the volume, it is hoped, will find a worthy if not a foremost place.

The great merit of a book by a single author is the sense of proportion appertaining to the completed work. Properly conceived and executed, it may be compared to any work of art. The sculptor gives prominence to the distinctive features of the subject, without sacrificing the smaller characteristics; all are in due proportion and the presentation is an artistic whole. So is it with a fine architectural drawing. Reference has been made to the completeness of Taylor's book in this respect, a result such as only could be achieved by a single author, and in this he displayed the attributes of an artist. Dr. Nixon in his paper on "The Debt of Medicine to the Fine Arts," read before the Section of the History of Medicine, remarked that "the progress in medicine has been won by those who, like artists, being richly endowed by nature with keen gifts of perception, have retained those gifts unimpaired, together with the Hippocratic secret of vivid imagery." Now Taylor possessed artistic gifts of no mean order, as some of his original designs in pen and ink testify, and he possessed imagination. Having thus the gifts of an artist, he produced such a work as only an artist could.

The appreciation by the writer of the obituary notice in the *Lancet*—one better acquainted with books on medicine than can be claimed by a surgeon—will convey the general opinion on the

Practice. After recalling Taylor's wide knowledge of medicine and his long hospital experience, he writes as follows :—

" All this fresh clinical and personal experience enabled him to write out of the fullness and personal knowledge the text-book, which has been the familiar friend of successive generations of medical students up to the appearance of the eleventh edition, less than two years before his death.

" The predominant features of Taylor's text-book are from the beginning, and in all its stages, first, the sense of balance which caused him to give the fullest consideration to the commoner diseases, leaving the rarities to be briefly treated, though with adequate proportion; and secondly its clearness. In so far as clearness leads to easy reading, it is apt to lead to easy forgetting, but the real salients of disease stick out from Taylor's *Practice of Medicine* and refuse to be forgotten, and to this day the work remains a valuable manual for students."

When Taylor's *Practice* was published in 1890 the two leading text-books were those by Bristowe and Frederick Roberts. The former made its first appearance in 1876 and the seventh edition, which was, I believe, the last, in the same year as Taylor's first. The second edition of Roberts' hand-book was published in 1876, the ninth in 1894, and after eleven years the tenth. Osler's first edition appeared in 1892, two years after Taylor's, and with intervals of three and four years successive editions followed up to the ninth in 1920. Taylor's would appear to be the only work of its kind to pass through eleven editions under the sole supervision of the original author. The *Practice* was translated into Italian.

Taylor's contributions to medical literature other than his *Practice of Medicine* were numerous and valuable, and are contained in the Transactions of the medical societies and the Journals, and especially in the *Guy's Reports*, to which he was a frequent contributor. Altogether there are one hundred and sixty-nine articles to his credit, dealing with clinical medicine and morbid anatomy, spread over a period of forty-seven years. These communications represent conscientious and disinterested work, undertaken with no other idea than the advancement of knowledge. " This quality of disinterestedness is," as has been well said, " the noblest possession of science. So long as it is maintained unsullied, the faith which millions to-day repose in the exercise of human reason as the cure of human ills will not fail of justification."

In endeavouring to portray a character, one needs, besides a sympathetic understanding, the eye of an eagle, the brush of

an artist, and the pen of a ready writer. Denied these possessions, one can only sketch out the main features. He was known to all connected with Guy's for half a century, and those who read this all too imperfect memoir and who have their own recollections of their old teacher or colleague will be able to fill in the gaps. Mention has been made of his well-balanced mind, which enabled him to form an accurate and well-sifted opinion; his sense of proportion; his sense of humour, and to these must be added sound common-sense.

As a teacher Taylor was exact, carrying accuracy perhaps farther than was possible for the average uninstructed man to appreciate. When discussing a case at the bedside, he would balance the pros and cons so nicely, exhibiting in this way the operation of his own mind, as to leave the student in some perplexity as to what the final judgment really was. These discussions would be interspersed with facts which, important as they might be to himself in arriving at a complete presentation of the case, would often appear to the listener irrelevant. His mind was cast in too legal a mould to permit of his ignoring doubtful points, and thus the discussion was apt to be overloaded with too much detail. Such mental qualities were of the greatest value in a discussion with the equally informed, as will be shown later, but, in teaching the elements of medicine, tended to produce confusion in the minds of the younger students. Thus Taylor was a good instructor of the mind, he showed how it operated, and while the method was not successful in the teaching of clinical medicine to the younger men, to the senior, who could follow the analysis, it was of inestimable value.

As an examiner Taylor, if sometimes exacting, was always courteous and fair, not so formidable as to prevent a candidate from doing himself justice, and yet too shrewd to allow the unprepared man to slip through the net.

To convey the impression his teaching had upon his pupils, I cannot do better than produce the appreciation written for the *Lancet* by one of his House Physicians, the late Dr. Fortescue Brickdale of Bristol.

"To his junior clerk he was a critical and somewhat severe master, to his senior clerk an erudite but rather mystifying teacher, to his house physician a source of lifelong inspiration in the intricate pros and cons of clinical medicine. As evidence of the remarkable esteem in which he was held by his house physicians, I may mention the imposing concourse which assembled at Guy's to accompany him in his last round of the wards.

"The source of his intellectual influences lay in two closely interwoven characteristics, his infinite care in the mastery of detail, and his devotion to truth. His mind was always collecting, balancing, and weighing evidence, and his clinical conclusions were consequently extraordinarily illuminating for those who understood his methods; his opinion was so nicely poised that the slight touch which he gave to the scale, one way or the other, might require considerable experience for its appreciation.

"All this does and does not come out in his *Practice of Medicine*. To the student this work appears concise and dogmatic, but to those who know his care in expression each statement is a summing-up of an extensive experience and an elaborate process of reasoning. I cannot, of course, speak of the value set upon his professional opinion by his colleagues, but I may say that I have often been struck by the way in which they all seemed to rely on him in times of personal sickness. To those who knew him well I believe Sir Frederick Taylor's intellectual capacity was equalled if not overshadowed by his other qualities. His exactitude was moral as well as mental, his kindliness severely simple and eminently practical; he had a well-developed sense of humour and a great faculty of unbending with his juniors, to many of whom he was not only a professional and personal example, but a beloved and valued friend."

An unsigned appreciation from one of his colleagues, which bears upon his teaching, I take from the *British Medical Journal* of December 18, 1920.

"The most striking things about him were his exceptional ability, his power of hard work, and his conscientious devotion to his duty. He never failed to attend his wards punctually, he never curtailed his rounds; indeed they were sometimes too long for the less enthusiastic of his followers. The chief characteristic of his teaching was his insistence on accuracy in fundamentals, such as physical signs, and his trenchant criticism of inaccuracy in others. He was an observant, highly skilled and far-seeing physician; his diagnosis was rarely at fault. He was a trifle austere, and students were inclined to feel a little afraid of him on first acquaintance, but this wore off when, as was always the case, they found he was anxious to do all he could to help them. Throughout his life he upheld the best traditions of his predecessors, and by his example, his industry and his teaching maintained the high ideals of the Hospital and its medical school, which was fortunate in having in him a man

who never sought popularity outside his profession, but who made it his life's occupation to strive hard for its good."

His powers of analysis and his attention to detail were of the greatest value when discussing a problem with a colleague, more especially as to the advisability of an operation. No aspect was left unexamined, the clinical facts were marshalled in due order, the value of each was assessed, due weight was given to the views of others, and whatever course was adopted, one felt that no important symptom had been overlooked.

I was associated with Taylor for some eight years in the handling of the cases in his wards having a surgical bearing, and had therefore many opportunities of appreciating his wide knowledge, his intimate acquaintance with morbid anatomy, and his penetrating and exhaustive study of clinical medicine. His open-mindedness on these occasions was conspicuous; did the surgeon hold a strong opinion as to the advisability of an operation while he was himself doubtful, Taylor at once yielded, while, on the other hand, were the surgeon doubtful, while Taylor saw the way, one felt secure in carrying out his wishes. The harmony of such co-operation was never interrupted by a jarring note, and the association remains as an example of what consultation really means. It was during these years that abdominal exploration began, and we had to learn when to interfere and how far to go. Taylor was present at operations whenever possible, that he might see the findings and learn the living pathology. To this end he spared neither time nor energy, and even insisted on being summoned at night to acute cases. In this way he became familiar with the varying conditions, could revise his diagnoses, and was able to give valuable advice, especially when the findings were not those expected. He acquired with the other physicians at Guy's, who adopted the same practice, a knowledge of surgery unsurpassed, I believe, by any similar group in London. At operations in private, where we often met, he was an expert assistant.

Reference has been made to his business capacities, especially in regard to the Medical School, but a word must be added as to the part he took in the general administration of the Hospital. He served on almost all committees of importance, took an active part in the promotion of the residential college, and on becoming senior physician presided over the monthly meetings of the staff. Here he was seen at his best, speaking little if at all during the debate, except when keeping others to the point, but, should discussion become heated, he would show by some remark its humorous aspect, or by some shrewd question

switch the discussion on to a better line. Finally, his summary was always excellent, and he never unduly used the authority of the chair.

Taylor was proficient in all manly exercises and sports. As a student he played football and was a good swimmer, and later he played a sound game of lawn tennis. It was at racquets that his rapid decision and lithe movement showed at their best. This game he played at Bethlem with his friends Savage, Bernard Pitts and Makine. Later on he took up fencing, again in association with Savage, and thus kept himself in good form. Golf he enjoyed in his holidays, but in this, like many others who only play occasionally, he never excelled.

Before his marriage he climbed the Alps for six seasons in company with his colleague Howse, mostly without guides. He tells of this himself in the memoir of Howse he wrote in Volume LXIX of these *Reports*, from which one gathers the keen enjoyment they shared on their excursions in the Alps. He gives all the credit of the preparations to his companion, but Howse would, I know, from what he has said, have attributed much of the success of these expeditions to the steadiness and resource of the man at the other end of the rope.

On his first visit to the wards after these holidays with sunburnt face and peeling nose, he was full of the joy of the experience and was wont to relate some of the most stirring incidents.

Taylor had a true artistic strain; he was facile with his pencil, and his etchings and water-colour sketches were above the average for an amateur. Though he did not play an instrument, he understood and appreciated good music. He was an accomplished whist-player, and later was quite as good at bridge.

It is hardly necessary to say to those who know his *Practice* that he was widely read in medicine. And in general literature his knowledge was the envy of some of us, while his retentive memory enabled him to recall passages with facility. He was not happy as a speaker before a large audience, his voice having small carrying power, but at Society meetings, where he was easily heard, the matter of his remarks was always informing, and his views were clearly expressed.

Taylor really enjoyed life. His bright outlook and his sense of humour, apt repartee and witty turn to a conversation, together with his knowledge of natural history and his appreciation of colour and cloud effects, made him a delightful companion.

In consultation he maintained his opinion with firmness and perfect courtesy, for his inbred politeness, springing from right-

heartedness and kindly feeling, made it impossible for him to wound another by look or word. In his professional life he presented in a high degree the sterling hard qualities of a true professional honesty.

Taylor made some close friendships and had many acquaintances both within and outside the profession. Amongst his colleagues I think he was most intimate with Howse, Hilton Fagge, Goodhart, Savage, Mahomed and Higgins, and with all the others he was on the most friendly terms. His advice was sought in times of sickness by medical friends, who knew his accuracy in diagnosis and were sure of unremitting care and attention, while his sympathy was just of the sort that men appreciate. Of a sensitive nature himself, he was quickly responsive to the suffering of others, whether bodily or mental.

On the more intimate subjects of life Taylor, I should say, showed a studied reserve; he did not reveal to others the deeper currents of belief which guided his life. When, as with him, action displays truthfulness, and a man really is what he purposes to be, other form of expression becomes unnecessary. Character, says Smiles, is the " glory of life," and those who knew Taylor's many sterling qualities will not deny him this possession.

When the rumour got abroad that our colleague was engaged to be married, we were all delighted, for he had won the esteem and friendship of everyone, and we rejoiced at the prospect of his happiness. I cannot recall any other occasion in which a wedding present was made by the whole staff. This signal mark of regard took the form of a set of silver candelabra. It was alike a personal tribute and a recognition of his unselfish devotion to the welfare of the Medical School. He was married on October 31, 1884, to Miss Helen Manby, daughter of Frederick Manby, Esq., of East Rudham, Norfolk. His daughter, who has inherited her father's artistic taste, and is known as a miniature painter, survives him, and one son, the holder of the baronetcy.

Sensitive himself, he was ever regardful of the sensibilities of others and never said a word which could wound the feelings of another. Disasters fall heavily on such a nature, and the Great War did not spare his family circle. In 1916 his second son, Harold, fell in France, a blow of double severity, for the overwhelming grief of the mother of this gallant boy added to his own distress. Then in the following year came the death of his wife, a bereavement which crushed his sensitive nature to the uttermost. During this period he was called upon to discharge the duties of President of the Royal College of Physicians, a position demanding great capacity for leadership. Such a task presented no difficulties to one with his experience

of the office of chairman of committee, and with his knowledge of business, but it was rendered onerous because of the cloud of sorrow which then overshadowed him. Then came the baronetcy, a distinction he had looked to his wife to share, which without her association was robbed of more than half its worth. In the latter part of 1917 and the early part of the following year he was occupied in the preparation of the eleventh edition of his text-book, which was acknowledged to be a painstaking revision.

These manifold cares and anxieties bore down a nature, long accustomed to dominate many a situation, demanding courage, strength of will, and self-control, and brought about the illness which compelled his retirement from active life. Thus passed one who was a true friend, a single-minded gentleman, a man who devoted himself to the Hospital and School he served so long and so well.

The concluding remarks of the obituary in the *Lancet*, representing an appreciation from outside Guy's, will fitly close this memoir :—

" This is only a brief record of a strenuous and valuable career, the termination of which at the age of seventy-three may still be considered untimely, for he was in the full tide of his activities when the illness struck him from which he never recovered. There is no doubt that the war affected him bitterly; his private sorrows and his public responsibilities were grievously heavy. He secured a place in the history of contemporary medicine by his single-minded devotion to his calling, and this is his best epitaph."

THE SPECTROSCOPIC TEST FOR BLOOD IN FÆCES

By J. H. RYFFEL, B.Ch., Chemical Pathologist, Guy's Hospital, and W. W. PAYNE, M.B., B.S., Anderson Demonstrator, Guy's Hospital.

(From the Laboratory of Clinical Chemistry, Guy's Hospital.)

A PAPER by J. R. Bell in the January number of these *Reports* dealt generally with the subject of blood in fæces. Here we propose to deal with the spectroscopic test in further detail.

When fæces containing blood are extracted with acetic acid and ether, two spectra may appear, namely, those of acid hæmatin and hæmatoporphyrin. Acid hæmatin is derived from hæmoglobin as such, or not so much altered as to have lost the iron it contains. The spectrum, being characteristic but not sensitive, signifies the presence of a considerable amount of blood, far more than would be present in the fæces as a result of taking a normal diet.

The tests usually employed for blood, such as the guaiac, benzidine and phenolphthalin tests, all employ a substance which, being colourless or nearly so, is converted to a coloured substance on oxidation, such oxidation taking place with hydrogen peroxide and a carrier, but not with hydrogen peroxide alone. With fæces the carrier is hæmatin in different forms according to the method of preparation, but other substances, such as iron and copper salts in solution and iodides, will also act as carriers, so that these have to be excluded. The iron sulphide in the fæces, when iron is taken by the mouth, does not, however, act appreciably as a source of error, presumably because it remains insoluble. The guaiac group of tests is much more sensitive than the spectrum of acid hæmatin, but obviously less distinctive.

Hæmatoporphyrin, the pigment obtained from hæmoglobin by the use of strong acids, does not contain iron and does not give the guaiac group of tests, so that, when it is present in the fæcal extract, it shows that at any rate some of the blood has undergone further change and would not be available for giving the guaiac tests. In this sense hæmatoporphyrin is complementary to acid hæmatin and the guaiac group.

How the change to hæmatoporphyrin is brought about is

uncertain. It might take place actually in the gut, or some product might be absorbed from which the liver forms hæmatoporphyrin, which is then excreted in the bile. The transformation to hæmatoporphyrin is most marked in moderate bleeding from the mouth, stomach or small intestine, and takes place also in bleeding from the cæcum or colon, but not in bleeding from the anal canal. In acute ulcerative colitis, when the stools are frequent and fluid and contain visible red corpuscles and pus cells, no hæmatoporphyrin is seen, but, as the acute condition passes off and the stools become more formed, there is more time for changes to take place, and hæmatoporphyrin appears at about the same time that actual red cells are no longer visible in large numbers. That any quantity of hæmoglobin derivative should under these conditions be absorbed from the large gut would appear improbable, but, on the other hand, attempts to transform hæmoglobin to hæmatoporphyrin by incubation with fæces, with or without added trypsin, have up to now failed, the resulting material yielding on extraction acid hæmatin and no hæmatoporphyrin.

Whatever the actual means of transformation, when there is sufficient time for the change, some of the blood is certainly transformed to yield hæmatoporphyrin, but this is not the only possible source of this substance in the fæcal extract. Thus the authors have occasionally found hæmatoporphyrin in the fæces of cases of Addison's anæmia, when the guaiac tests were negative and there was no reason to suppose that there was any hæmorrhage into the alimentary canal, and porphyrins have been found in the fæces of cases of hydroa æstivale. Such instances are rare, but it is best to rely on the guaiac tests in conjunction with the spectroscopic after suitable dieting, employing the spectroscopic test alone without dieting merely as a preliminary. Specimens occur in which the blood has been so transformed that hæmatoporphyrin is positive while the guaiac tests are negative. This will be found at the end of a period of bleeding, the hæmatoporphyrin persisting longer than the product containing iron. Earlier specimens would have shown both tests, and later ones will do so if bleeding starts afresh.

Hæmatoporphyrin is not recognisable in the extract from normal fæces. On one occasion a highly pigmented extract was obtained, which gave a strong guaiac test and showed a doubtful and faint hæmatoporphyrin band, but this was the only occasion on which the spectrum of hæmatoporphyrin has not been definitely absent.* To judge by the guaiac test, the

* *Vide* also J. R. Bell: *Guy's Hospital Reports*, lxxiii. 20, 1923.

blood in the meat taken in the diet of certain normal individuals should be sufficient to yield the spectrum of hæmatoporphyrin, so that blood in cooked meat would appear not to undergo the change to any appreciable extent. Raw meat has not been tried.

The change to hæmatoporphyrin appears to be inhibited by large quantities of mineral substances. Thus in Sippy's method of treating gastric and duodenal ulcers repeated doses of magnesia, calcium carbonate and bismuth carbonates are given, which amount in the course of the day to a large quantity. As a result the fæces are bulky, heavy, have a greyish colour and sometimes effervesce with acid. These fæces may yield good guaiac tests and even the spectrum of acid hæmatin, but that of hæmatoporphyrin is generally absent. Where the dosage of mineral material is smaller, the fæces may be more normal in appearance and may contain hæmatoporphyrin.

Method of Examination

The most suitable spectroscope is a direct-vision one of the Zeiss type with adjustable slit and a well-marked green region. The small diffraction spectroscopes have not an adjustable slit and give rather a diffuse spectrum, but are better than a poor specimen of prismatic spectroscope. As the Fraunhöfer lines are confusing, it is better to use artificial light. An incandescent gas-mantle is excellent; so is an opalescent electric globe, if bright enough. For the preparation of the extract thick test-tubes, 7 inches by 1 inch, are used, and for the later manipulation the flat-bottomed glass tubes 3 inches by 1 inch, often used for fæcal specimens, are convenient.

A mass of solid fæces about the size of a large bean is taken and mixed with water, or a correspondingly larger amount of a looser specimen is used without the addition of water. Rather over an equal volume of glacial acetic acid is added and well mixed with a glass rod. Then a volume of ether fully equal to that of the mixture is added and well mixed. The water, acetic acid and ether mix to a uniform liquid, which is thus particularly suitable for the extraction of blood pigments. On the addition of water the ether floats to the top of the tube and is generally clear, the solid matters remaining with the water. If the ether does not separate on the addition of water, not enough ether has been added. Specimens rich in mucus or paraffin are specially troublesome, as some emulsification is liable to occur. This may be broken down by adding glacial acetic acid cautiously. Part of the ether extract is then used for

the guaiac or benzidine test, or the latter test may be applied to the original fæces by a different technique. If the extract be examined at this stage, hæmatoporphyrin will be present in the alkaline form. It is, however, better to transform it to acid hæmatoporphyrin, as the spectrum is more marked and it is thereby separated from other pigments. For this purpose as much of the ether extract as possible is decanted into one of the fæces tubes, strong hydrochloric acid, diluted to four times its volume with water, is added, and the fluids mixed by pouring to and fro from this tube to another. On standing, the ether and water layers separate rapidly, the upper or ether layer containing acid hæmatin and chlorophyll, the lower or water layer acid hæmatoporphyrin, while both contain stercobilin. If too much diluted hydrochloric acid is used, the hæmatoporphyrin will be unnecessarily dilute; if too little, a water layer too narrow for examination will be obtained.

The spectrum of acid hæmatoporphyrin shows a narrow band in the orange and a well-marked rather broad band in the yellow green. Unless the spectrum is a strong one, the green band alone is visible. The spectrum of acid hæmatin shows a broad band in the red and another in the green, slightly broader than that of acid hæmatoporphyrin and more towards the blue end of the spectrum. Acid hæmatin shows a further green band as well, but this is obscured by the absorption due to stercobilin. Chlorophyll shows a many-banded spectrum, of which the most conspicuous is a band in the far red. As these bands interfere with the spectrum of acid hæmatin, it is best to exclude chlorophyll from the diet where possible.

The different combinations which may be observed are summarised as follows :—

(*A*) *Patient has not been dieted.*—Acid hæmatin shows bleeding with certainty; hæmatoporphyrin shows probable bleeding. Chlorophyll is usually present.

(*B*) *Patient has been dieted.*

1. *Acid hæmatin alone.*—In large amount—acute hæmorrhage; in smaller amount—bleeding from rectum or anal canal.

2. *Acid hæmatin and hæmatoporphyrin together.*—This is the common condition when the amount of blood is considerable but not excessively large. The hæmatoporphyrin shows that the bleeding is not exclusively anal, but may be colonic.

3. *Hæmatoporphyrin present without acid hæmatin, the guaiac tests being positive.*—Of the same significance as 2, but the amount of blood is less.

4. *Hæmatoporphyrin present alone, guaiac tests being negative.* —Either a remnant of previous bleeding or hepatogenous hæmatoporphyrin.

5. *Guaiac tests positive, no blood spectrum.*—The amount of blood may be too small for spectra, or it may be protected in some way, *e. g.* by Sippy's diet. There may be slight anal bleeding, or dieting may have been insufficient. In the last case chlorophyll may be visible.

The following is an analysis of results obtained during 1921, in which the diagnosis was determined at operation or at post-mortem examination, together with the results of 24 cases collected by Dr. J. F. Venables from the records at New Lodge Clinic during the last eighteen months, in which the diagnoses were confirmed at operation.

Pyloric ulcers.—6 cases. Blood spectrum in 5.

Gastric ulcers.—12 cases. Blood spectrum in 8. Guaiac not positive in 6. Of the remaining 4 the guaiac test was positive in 2.

Duodenal ulcers.—11 cases. Blood spectrum in 6. Guaiac test positive in 1 out of remaining 5.

Carcinoma of stomach.—11 cases. Hæmatoporphyrin in 10; acid hæmatin in 8; guaiac test positive in 10.

Carcinoma of pancreas.—4 cases. Blood spectrum in 3.

Carcinoma of colon or rectum.—6 cases. Hæmatoporphyrin in 6; acid hæmatin in 1.

Jejunal ulcer following gastrojejunostomy.—3 cases. Hæmatoporphyrin and positive guaiac test in 3.

Gall stones.—2 cases. Negative in 1. Hæmatoporphyrin in 1; this case had an old gastrojejunostomy and many adhesions.

Chronic appendicitis.—3 cases. Negative in 2. Hæmatoporphyrin in 1, in which an abscess had ruptured into the ileum.

Chronic duodenal ileus.—1 case. Negative.

Diverticulitis.—1 case. Positive hæmatoporphyrin and guaiac test.

No lesion of alimentary tract found.—12 cases. Hæmatoporphyrin with positive guaiac test in 4, of which 1 showed acid hæmatin as well.

In addition the crater of an ulcer was demonstrated by x-rays without operation in 8 cases, of which 5 showed a blood spectrum.

Cases in which less definite evidence of ulceration was obtained have not been included, but for comparison two indefinite groups may be mentioned.

Visceroptosis or constipation.—18 cases. Hæmatoporphyrin in 3.

All other investigations negative.—19 cases. Hæmatoporphyrin definite in 2, faintly positive in 2 more.

The above cases are not sufficiently numerous to admit of mathematical analysis, but from these and more recent cases, which are not tabulated, one may come to the general conclusion, that cases of pyloric ulcer, and growths of the stomach and large intestine show hæmorrhage with remarkable consistency. Gastric ulcers are more irregular in their bleeding. Duodenal ulcers show a group in which hæmorrhage is a striking symptom, and another group in which hæmorrhage is slight, irregular or lacking. Finally there is an indefinite group of cases, in which evidence of hæmorrhage into the alimentary canal is occasionally found, but no evidence is obtained from other sources as to the site of bleeding.

OCCULT BLOOD IN THE FÆCES

By ADOLPHE ABRAHAMS, O.B.E., M.D., Assistant Physician, Westminster Hospital.

DR. J. R. BELL'S kindly reference to my own interest and work in the subject with which he deals in the January number of the *Reports*, and his welcome confirmation of certain conclusions to which I have arrived, encourage me to accept with alacrity an invitation to contribute a short note.

I cannot claim a laboratory experience of any considerable extent, and my attraction towards the investigation has been mainly a clinical one. Furthermore, such experimental subjects as I have been privileged to enlist as volunteers or employ *malgré eux* have necessarily been patients confined to bed for some pathological condition other than a gastro-intestinal disorder, and for whom a milk diet, or at any rate a hæmoglobin-free diet, was a routine. It is not altogether unlikely that certain pathological states may enter some complicating factor.

I must first of all express my appreciation of Dr. Bell's endorsement of my observation that the smallest quantity of blood given by mouth in a single dose, which will produce a positive benzidine reaction in the fæces, is between 0·5 c.c. and 1 c.c. Such an experiment is so obvious a one that it must occur to the mind of almost any researcher, and in implying priority to the extent that I believe I first described this procedure, I claim neither originality nor ingenuity. But I certainly have been surprised to meet the opposition which this observation has induced. I was informed, for example, that the faintest trace of blood thus entering the alimentary canal would give an intensely positive reaction, and that such an experiment as I had conducted did not reproduce the condition of a bleeding ulcer, which it never claimed to do.

Bell suggests that it is quite possible that 1 c.c. of blood could be swallowed within a comparatively short time from severe gingivitis and inflammatory conditions of the nasopharynx, but that minor degrees of these conditions can hardly be held responsible for erroneous results. With this I heartily agree, but I feel that another investigation which I had hoped to complete, but in which I have been denied opportunity, would be of some interest, namely, to administer not one single large dose but many tiny doses throughout the day. It is possible that in the aggregate after such administration, less than 1 c.c. would be required to yield a consistently positive result.

Bell recommends the elimination of iron compounds and iodides during investigation, and I see that Dr. J. H. Ryffel repeats this injunction—with the addition of copper salts. Neither gives any actual results in experiments on this head, and my recollection is that I investigated the subject from this standpoint and included several other drugs and substances, but did not find any vitiation of the test from their inclusion. But unfortunately I can give no actual results in simply quoting from memory. I remember one amusing discrepancy in a patient under investigation in a nursing home. His fæces gave an intense benzidine reaction whenever they were examined, and clinical medicine would, it seemed, have to yield to chemical pathology in a diagnosis of malignant disease. Only by accident did I discover that the patient was in the habit of taking several pills of potassium permanganate each day, which he had prescribed for himself on some therapeutic principle of his own.

I have mentioned the necessity of employing patients who were suffering from some pathological disorder. In one or two instances when those with acute infections were employed, being conveniently restricted to a milk diet, a strongly positive benzidine reaction was obtained. It seems not improbable that the fæces of such patients may contain oxidases which, like hæmoglobin and its derivatives, and unlike those present in food-stuffs, are not destroyed by heat.

Bell does not emphasise—and doubtless he thinks there is no necessity to do so—the importance of securing as a positive result an unmistakably *blue* colour. Of course "blue-green" merges into "green," and a doubtful reaction may be interpreted as blue-positive or green-negative according to one's predilections. The usual fæcal emulsion has itself not infrequently a dirty green colour, for which reason I feel one must insist upon a blue element being unmistakable. And as a final precaution I would insist on scrupulous cleanliness. This proviso would not appeal to the laboratory worker, drilled and instinctively or automatically "clean," but I am thinking of the clinician employing the test in his daily routine. Contamination occurs so readily. Fresh test-tubes every time the test is undertaken sounds an extravagance, but it will pay to be accurate and unequivocal in this sort of work. And may I be forgiven for saying that the reagents themselves should be regularly tested against preparations which are known to be absolutely free from oxidases, or the discomfiting experience of my own may be repeated of a positive benzidine test occurring spontaneously?

CONTRIBUTIONS TO THE CLINICAL STUDY OF INTRACRANIAL ANEURYSMS

I

By C. P. SYMONDS, M.D., Assistant Physician for Nervous Diseases, Guy's Hospital.

INTRACRANIAL aneurysms discovered in the post-mortem room have always appeared sufficiently remarkable to excite comment, so that many isolated case reports have been published from time to time. It is, however, to the credit of Sir William Gull that he first recognised the comparative frequency of the condition. The opening paragraph of his paper in the Guy's Hospital Reports of 1859 [1] contains much that is pertinent to-day:

"Aneurism of the cerebral vessels has been regarded as a disease of extreme rarity, and judging by the scanty records of it, we should conclude that the opinion was true. This apparent rarity, however, like all negative conclusions, is doubtful, and I think there is the more reason to suspect it as only apparent and due to careless inquiry since the discovery of these cases has been much more frequent during the last ten years. There are several reasons why intracranial aneurism is likely to be overlooked. First of all, as here hinted at, it has not been looked for, and it is notorious that the eye can see only that it brings with it the aptitude to see. Again, when death occurs from rupture of the sac, recent coagula may so imbed and conceal it that unless strictly looked for it will not be found, for the sac is often small, and thin and transparent, except at the point of rupture. Further, also, when death has taken place from changes around the aneurism, as by pressure or softening, the sac itself may present such appearances that unless a minute dissection be made of it, its true nature may not be discovered. Whenever young persons die with symptoms of ingravescent apoplexy, and after death large effusion of blood is found, especially if the effusion be over the surface of the brain in the meshes of the pia mater, the presence of an aneurism is probable."

Since the publication of this paper there have appeared in the English and German literature many important contributions to the subject, notably those of Beadles,[2] Wichern,[3] Reinhardt,[4]

von Jaksch,[5] Fearnsides [6] and Turnbull.[7] Those of Fearnsides and Turnbull are of considerable interest as throwing light upon the pathology of the condition, their conclusions being, first that syphilis, contrary to former beliefs, is an exceedingly rare cause of intracranial aneurysm; and second that, besides those well-recognised instances in which the condition is associated with infective endocarditis, or cerebral arteriosclerosis, there is another group of cases frequently occurring in young persons, in which the aneurysm is congenital, or depends upon the combined effects of increased blood pressure and a congenital weakness of the arterial wall at certain points.

As to the clinical aspect of this condition, it appears from the statistical records that in many cases the patient has been admitted to hospital moribund with the symptoms of a grave cerebral illness, and the diagnosis has been made after death.

In about one-third of the cases, however, symptoms of intracranial disease have existed for months, or even years, before the fatal issue. Yet Fearnsides, writing in 1916, concluded that there was nothing to add to Gull's original dictum that "although we may from the circumstances sometimes suspect the presence of aneurism within the cranium, we have, at the best, no symptoms upon which to ground more than a probable diagnosis."

In recording the clinical histories of five cases diagnosed as intracranial aneurysm which have come under my observation during the past two years, it is my purpose to draw attention to the possibility of an accurate diagnosis of the condition during life. In each case the diagnosis was made at the bedside, and in three out of the five it was subsequently confirmed at the post-mortem. The remaining two patients are still alive, but I have little doubt that in these cases also time will disclose an aneurysm at the base of the brain. My personal interest in the condition was first aroused by the following case which I saw at Prof. Harvey Cushing's clinic in August 1920 :—

Case 1.—B. J. H., a married woman, aged 52, was admitted to the medical wards of the Peter Bent Brigham Hospital on August 30, 1920, complaining of headache and vomiting. She was thought to have a cerebral tumour and was transferred to the service of Dr. Cushing, who kindly allowed me to make the following notes : —

Family history.—Her father died of some intracranial disease; her mother of heart trouble.

Personal history.—Up to the time from which she dates her present illness her general health has been good. She had an attack of malaria in 1895. She has given birth to four children, of whom three are alive and well, and her last pregnancy

eighteen years ago terminated in a miscarriage, since when she has suffered with prolapsus uteri. For the past seven years she has noticed shortness of breath on exertion, which was ascribed by her physician to high blood pressure, has suffered from occasional headaches, and has had attacks of faintness in which she felt as if she were going to be paralysed. Menopause in November 1919.

She has never used alcohol or tobacco, and there is no history of venereal disease.

She had earache as a child, but never any otorrhœa.

Present illness.—In April 1919 the patient had an illness, causing her to take to her bed for four weeks, which was diagnosed as influenza. With this was associated severe headache, pain in the back of the neck radiating down into her back, and vomiting. There was also tinnitus in the right ear, and with it partial deafness. During convalescence she was giddy and her gait was unsteady for some time.

Since this illness she has suffered with severe headaches in the right frontal region: these are intermittent, but have been increasing in severity. In December 1919 she first noticed diplopia, which has since been permanent. She has also complained of failing memory and diminished visual acuity.

About August 14, 1920, she was seized with a sudden severe pain in the right supra-orbital region, which has persisted: for the first three days this was accompanied by frequent vomiting. A few days after the onset of this attack it was noted that her right eyelid was drooping and that there was some protrusion of the eyeball. No history could be obtained of convulsions, general or focal, nor of uncinate seizures.

On examination. General physical condition.—The patient is a well-developed woman weighing 152 lbs. The systolic blood pressure is 185 mm. Hg., the diastolic 110 mm. Hg. The aortic second sound at the base is accentuated. There is prolapsus uteri. Urine S.G. 1012. No albumen. An occasional hyaline cast. Temperature 99·8°. Pulse 88. Respirations 20. Wassermann in blood negative.

Central nervous system.—The mental state is dominated by the reiterated complaint of pain in the right eye and brow, for which she asks relief. She is in good contact with her environment, but thought is slow, and she shows difficulty in remembering the chronological sequence of her story—a defect in memory which she herself realises.

Visual acuity cannot be tested (owing to lack of co-operation), nor is it possible to obtain a chart of her visual fields, though these seem normal on rough testing. The right fundus oculi shows engorgement of the central vein, and blurring of the nasal margin of the disc. Lying immediately beneath the inferior branch of the temporal artery, two discs breadth from the disc, is a circumscribed white patch appearing about 4 mm. in diameter. The left fundus shows similar venous engorgement and blurring of the entire circumference of the disc. The

retinal arteries on both sides show a moderate degree of " silver wire " thickening.

Hearing.—Watch heard at normal distance on left; not heard on contact on the right. Air conduction better than bone conduction on both sides. Vibrations of a tuning-fork on the forehead lateralised to the left. Ear drums normal.

Sensations of smell and taste normal.

Cranial nerves.—There is complete right-sided ptosis at rest. Slight exophthalmos both sides, more marked on the right. The right pupil is larger than the left; it is a little irregular, and eccentric, being displaced inwards; it does not react to light or in accommodation. Left pupil regular and central and reacts normally. There is complete paralysis of all muscles innervated by the right third and fourth cranial nerves.

No other disturbance of extra-ocular movements, no affection of the 9th, 10th or 11th pairs. The tongue is protruded slightly to the left.

Sensory examination reveals no defect. The general *musculature* shows normal tone and power; no inco-ordination.

The deep *reflexes* are normal and equal throughout, the epigastrics and abdominals present and equal, the plantar responses flexor.

Sphincter control normal.

On the morning of September 2 she had a sudden severe exacerbation of her orbital pain, and lost consciousness for a period of twenty minutes. During this attack there was no convulsion, but the nurse noted that both eyes seemed to protrude further, and there was a profuse flow of tears from the right eye. After coming to her senses she continued moaning with pain. Shortly after midnight she again became unconscious; the pulse was 60 and the respiration of the Cheyne-Stokes type.

The same night she rallied, became conscious again, recognised people around her and talked quite freely. She complained of severe headache radiating down into the back of her neck on the right side. After this she again became unconscious.

During the morning of September 3 twitching movements were noted of the left leg, later of both legs. When seen at noon she was comatose, but made occasional movements of a purposive nature with the right arm. She also withdrew the right lower limb vigorously when the foot was pinched, but the left limbs remained motionless under any form of stimulation. The plantar response from the left sole was definitely extensor, on the right indefinite.

The fundi showed marked changes. On right the œdema

of the disc remained as before; in addition there were a few punctate hæmorrhages scattered about the retina. On left the edge of the disc was partly obscured by one of several large sub-retinal accumulations of blood. It was noted at the time that these had not the ragged outline usually seen in large retinal hæmorrhages.

As the patient roused a little from her coma it was possible to determine that her right external rectus was paralysed.

A right sub-temporal decompression was performed by Dr. Cushing the same afternoon. A tense dura was disclosed, which on being opened revealed recently clotted blood extending over the whole hemisphere and apparently coming from the base of the skull.

That night her temperature rose to 103 and she died early on the morning of September 4.

The autopsy was performed the same afternoon. On removing the brain the whole sub-dural and sub-arachnoid spaces at the base were found full of recently coagulated blood. This washed away easily under the tap, disclosing a small saccular aneurysm about 8 mm. in circumference at the junction of the right internal carotid and posterior communicating arteries. In the outer wall of this sac was a perforation the size of a pin's head. There was no evidence of old coagulation around the sac (see Fig. 1). Within the arachnoid sheath of the left optic nerve just in front of the chiasma lay a minute collection of extravasated blood about 2 mm. in diameter. In the sheath of the right optic nerve was a similar minute extravasation.

The right third nerve opposite the sac was thinned and showed a greyish-yellow colour in contrast with the normal clean pallor of the opposite side.

On reflecting the dura from the hemispheres one found thin layers of coagulum filling both sub-dural and sub-arachnoid spaces. On examining the basal vessels it was noted that there were many yellow atheromatous beads upon their walls, the distribution of which was as follows: both vertebrals for 1 cm. from their junction; the basilar for the first cm. of its course and the last half cm.; both posterior cerebrals up to the point of their disappearance, and especially at the points of issue from the basilar; the left internal carotid at its junction with the posterior communicating.

The heart weighed 360 grams, the myocardium and valves appearing to the naked eye normal. Some atheromatous patches were seen in the descending aorta. The mesenteric, iliac and renal vessels showed no signs of arteriosclerosis.

The kidneys weighed each 160 grams. The capsules stripped with some difficulty, leaving a slightly granular surface. The cortex of both was of about the same width, measuring 6–8 mm. At the upper pole of the right were several small retention cysts.

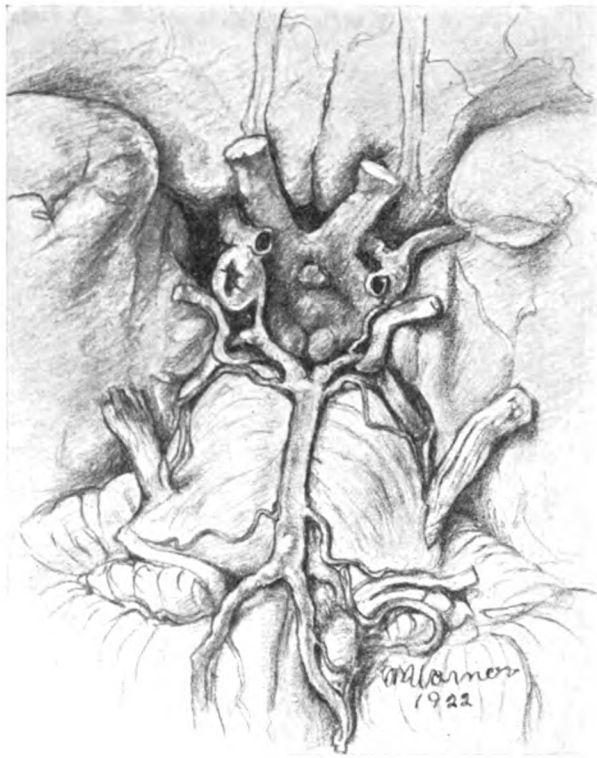

FIG. 1.

Case 1.—Drawing of the base of the brain, showing the aneurysm at the junction of right internal carotid and posterior communicating arteries.

In an analysis of this case it seems well to distinguish three groups of clinical signs and symptoms :—

(1) Those due to mechanical pressure upon surrounding structures—neighbourhood signs. These depended upon the localisation of the aneurysm rather than upon its nature.

(2) Those due to the disease which was the primary cause of the aneurysm.

(3) Those peculiar to the presence of the aneurysm itself.

(1) The neighbourhood signs in the present case were those

which may be produced by any tumour situated in or upon the outer wall of the cavernous sinus—a syndrome which has been frequently described in relation to growths in this situation.[8]

The actual sequence here was pain in the distribution of the ophthalmic division of the fifth, signs of paresis and finally paralysis of the third, exophthalmos, diminished visual acuity probably due to pressure upon the right optic nerve, paralysis of the fourth, paralysis of the sixth.

I have been able to find in the literature several case reports relating to aneurysms of the internal carotid in this precise situation, the details of which closely resemble those of the instance which I have just related. Those most clearly described are by Hutchinson,[9] Viets,[10] Fearnsides [6] (cases 30 and 31), Beadles [2] (page 325), Fisher,[11] and Reinhardt [4] (Case 1). Occasionally an aneurysm in this region arising from the inner wall of the artery may erode the wall of the sella turcica and by encroaching upon the pituitary body give rise to symptoms of dyspituaritism together with optic atrophy and hemianopia as in Bramwell's [12] and Mitchell's [13] cases.

(2) *Signs of the disease causing the aneurysm.*—There were present certain indications that the patient was suffering from cerebral arteriosclerosis. For some years she had suffered from dyspnœa on exertion, headaches and attacks of giddiness, which had been ascribed by her physician to high blood pressure. On examination her blood pressure of 185 was considerably above the normal, the retinal arteries showed silver wire thickening, and the mental condition was one which is not infrequently met with in cerebral arteriosclerosis, namely, a defective memory for recent events, of which the patient herself complained.

(3) *Signs and symptoms peculiarly due to the presence of an aneurysm.*—Of these without doubt the most frequent in all cases of intracranial aneurysms are signs due to the occurrence from time to time of sudden leakage from the sac.

In Case 1 there can be little doubt that the attack, which occurred in April 1919, of headache, vomiting and severe pain in the back of the neck, radiating down into the back, and which was at the time diagnosed as influenza, was in reality due to leakage of blood from the aneurysm into the sub-arachnoid space at the base of the brain with subsequent clotting, absorption and recovery.

The following two cases will serve to illustrate the clinical picture which results from such an occurrence.

Case 2.—Colonel E., aged 70, single, a retired officer of the Indian Medical Service, had led an active, busy life up to the date of the illness to be described.

On July 29, 1922, he was in his usual health. On the following morning, however, he complained to his landlady, on being called, that he had had a very bad night, with pain in the back of the neck. An hour or two later he was discovered lying in the bathroom in a dazed condition with a small scalp wound in the right parietal region.

He was conscious when found, and said that the pain in the back of the head had suddenly become intense, "something seemed to snap there," and he fell.

He was able to walk downstairs with support, went to bed, and stayed there for the next few days, though he got up to shave and wash. During this time he had a very foul, coated tongue, he was constipated, and "a little light-headed" at times. Besides the pain in the neck, he complained of considerable pain in his thighs, so that, for example, when he began to walk and bent his knees he would stop suddenly with the severity of it.

His condition slowly improved until August 10, when he had bacon and eggs for breakfast. He had had his bowels open and his tongue was clean.

At 12·15 a.m. on the 11th he again sent for a medical friend, complaining of intense pain in the back of the neck, which was arched backwards. Subsequently he became gradually unconscious.

When I first saw him the same afternoon he was in a state of coma with stertorous breathing. He lay with his head turned a little to the right. Both eyes were open, but the left lid a little lower than the right. The pupils were small, the left slightly the larger, and did not react to light. There was some external strabismus of the left eye. Slight weakness of the left face. The pulse was 48, the systolic blood pressure 150 mm. Hg. The peripheral arteries to the feel and the retinal arterioles to the view appeared to be in good condition.

On examination it was noted that there was definite backward rigidity of the neck. Kernig's sign was also present. He grimaced as if with pain when an attempt was made to carry the passive movement past a certain point.

In addition to this, there was some rigidity of the limbs. The upper limbs were flexed at the elbows and pronated, the lower limbs fully extended, feet arched and toes pointing downwards. There were occasional purposive movements of the right arm. In addition, involuntary movements were present, upon which I made the following note. "All the while there are involuntary twitching movements which are indistinguishable from the coarse fibrillations of progressive muscular atrophy or syringomyelia, and remind one of certain myoclonic phenomena seen in encephalitis lethargica. These twitchings are seen in all the muscles of the upper limbs (being especially noticeable in the right hand), in the abdominal muscles, and in the feet, especially the toes."

The comatose condition of the patient made sensory examina-

tion impossible. As to the reflexes, none of the tendon jerks could be obtained: both the plantar reflexes were extensor. He had retention of urine and catheterisation was necessary.

On August 12 he rallied in the early morning, became conscious, asked for water, and expressed a wish to pass urine, which he was able to do at will. At 10.30 a.m. he recognised and talked with his friends. At 3 p.m. he suddenly became unconscious again, and died six hours later.

The post-mortem performed the next day was limited to the brain. On removal of the skull and incision of the dura, the subdural space at the vertex seemed to contain free blood, but this was small in quantity and may have escaped from an accidental rent in the arachnoid. At the base there was no doubt that the blood had escaped into the subdural space, for it was thickly clotted in both temporal fossæ after the brain with the lepto-meninges had been removed.

The sub-arachnoid space over the greater part of the hemispheres contained no blood, but at the base this was abundant, obscuring all the vessels and nerves, covering the under surface of pons and medulla, and extending in a thick layer down the spinal canal as far as one could see. When the cervical cord was cut through for removal of the brain there was a considerable flow of blood from the spinal sub-arachnoid space.

After removal a stream of water was directed upon the clot at the base, and it was gradually wiped and teased away. About the right side of the pons and medulla it was especially adherent, and at the angle of junction of pons and medulla on the right side close to the origin of the 6th nerve was a hard oval clot the size of an almond. This was dislodged with difficulty, as it appeared to extend into the substance of the brain stem.

On cutting this hard clot across, I observed a small cavity in its centre, and this I am inclined to think represented the cavity of a minute aneurysm.

A sagittal section of the pons and medulla revealed a clot the size of a cherry stone to the right of the midline, which was directly continuous through the rent in the surface with the hard clot already described. The clot within the nervous substance was of a soft jelly-like consistency, and clearly of a date later than that of the external one. It seemed, therefore, as if the hæmorrhage into the medulla had been from the surface inwards rather than in the opposite direction. Unfortunately the suspected aneurysm and adjacent parts, which were needed for further examination, were by an oversight replaced within the cranium and lost.

The rest of the brain was of normal size and configuration, and on section showed no abnormality.

The cerebral arteries on the whole were in very good condition, with the exception of isolated plaques of atheroma in those of medium size, and extreme calcareous rigidity of the carotids.

In this case the nature and causation of the pain and stiffness in the neck, the pains in the thighs, and subsequently the positive Kernig's sign, are sufficiently obvious. They are the signs usually met with when the spinal nerve roots within the sub-arachnoid space are subject to irritation by foreign substances.

The explanation of the involuntary twitching movements is less clear. On account of their symmetry I am inclined to assign this symptom to irritation of the motor fibres in the anterior nerve roots.

Case 3.—Miss J., aged 52, a nursing sister at a Fever hospital, had always enjoyed good health with the exception of occasional headaches for the past few weeks.

On April 24, 1922, she began to feel unwell at lunch and did not want to finish her meal. Feeling rather faint she retired to her room, and then " suddenly there was a whirling feeling at the base of my skull, and something seemed to snap."

The resident medical officer being called, found her in a semi-conscious state, and ordered her to bed.

She gradually regained her senses, but then complained of intense headache, at first frontal, now (April 29) fronto-occipital and radiating down the back of the neck into the spine. There has been complaint at times of numbness in both hands. (This succeeded the pain in the back of the neck.) The temperature and pulse are shown in the chart (see Fig. 2).

When I saw her on April 29 she appeared a rather heavily-built woman, her face a little flushed, complaining of intense headache, almost oblivious to all else. She complained that movement increased the headache.

On examination the most noticeable feature was definite rigidity of the neck, with great complaint of pain on attempted flexion. Kernig's sign was absent. The nasal edge of the right optic disc was a little blurred, and the veins of both engorged. The functions of the cranial nerves and of the motor and sensory systems appeared normal. The plantar responses were on the right doubtful, on the left an occasional extensor reflex. Apart from this no alterations in the reflexes.

The tongue was very foul and coated. The blood pressure systolic 145 mm. Hg., and diastolic 80 mm. Hg., the retinal vessels very fair. No albuminuria.

In view of the fact that the patient was working at a fever hospital, I thought, in spite of points to the contrary, that this might be an anomalous case of cerebro-spinal fever.

I therefore performed lumbar puncture. The needle went in easily and there at once issued blood diluted with cerebro-spinal fluid, which at first appeared to be under pressure. Two specimens were collected in separate tubes, but the percentage of blood in each seemed to be about the same. Dr. Mann kindly examined the specimens for me and found that the proportion of white to red blood-cells was that of normal blood. No organisms were discovered.

A further lumbar puncture performed three days later again revealed evenly blood-stained cerebro-spinal fluid.

I saw the patient again on May 24. She had made considerable improvement, but was said to have been wandering a little in her mind. The headache had become progressively less severe and the neck stiffness had disappeared. The reflexes were normal except that the left plantar response could not be obtained.

On May 28 at 5 a.m. the resident medical officer was called to see her in an attack which resembled the initial one but was less severe. She complained of severe pain in the head, retched a little and was said to be " hyper-sensitive." After an injection of morphia these symptoms cleared up and she continued to make a slow and uneventful recovery.

Seen on November 2, 1922, she appeared to be in good health but was slow in answering questions. A friend who was with her stated that slowness of thought and action was the most noticeable relic of her illness, being foreign to her usual manner. She complained of occasional headaches. The left pupil was somewhat eccentric, being displaced inwards, and irregular in outline. The blood-pressure was systolic 155, diastolic 70 mm. Hg.

The similarity of the symptoms in these two cases is striking. Both patients after prodromal pains experienced the sensation of something snapping at the base of the skull. In both instances the initial loss of consciousness which attended the stroke was of brief duration, and was followed by a dazed condition in which the patient was said to be " light-headed " or " wandering." Both subsequently developed intense pain at the back of the neck associated with stiffness. In both cases after an interval of days there was a recurrence of symptoms leading in Case 2 to death, in Case 3 to recovery.

The autopsy in Case 2 and the deeply blood-stained cerebro-spinal fluid obtained from Case 3, make it clear that the cause of the symptoms in the two cases was the same—rupture of the wall of a vessel at the base of the brain with leakage into the sub-arachnoid space.

The relatively slight degree of loss of consciousness appears to have been due to the free passage of the effused blood into the arachnoid space surrounding the spinal cord, which prevented such an intracranial accumulation as would have caused compression of the brain with coma. In Case 2 when the hæmorrhage had recurred and the patient was within a few hours of death the transient recovery of consciousness was a remarkable feature. This point would seem to be of value in distinguishing such cases from those of intracerebral hæmorrhage, with which they are probably often confused.

In any case, as Wichern [3] observes, the appearance of pain and rigidity in the back of the neck shortly after an apoplectic seizure should arouse the suspicion of sub-arachnoid rather than intracerebral hæmorrhage.

The temperature chart in Case 3 (see Fig. 2) is of interest in that, together with the other symptoms, when the patient was seen on the fifth day of the illness, it aroused the suspicion of an infective meningitis. In the presence of such pyrexia, with complaint of headache and pains in the back and limbs, one can see the argument for the mistaken diagnosis of influenza which was made in the initial attack of Case 1.

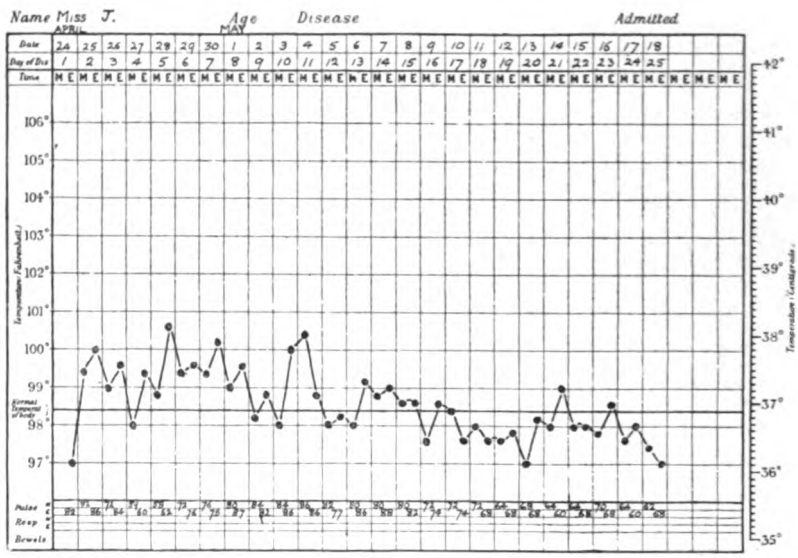

FIG. 2.

Case 3.--Temperature (by mouth) and pulse chart for first 25 days of illness.

From the study of Cases 2 and 3 it may be concluded that the signs and symptoms produced by hæmorrhage into the sub-arachnoid space at the base of the brain form a diagnostic picture the reality of which may be confirmed by lumbar puncture. Wichern,[3] Löwy,[14] and especially James Collier,[19] have already insisted upon this in relation to intracranial aneurysms. It must be remembered, however, that hæmorrhage into this space may also result from the rupture of a superficial vessel without the presence of an aneurysm, as the result of trauma, arteriosclerosis or diseases of the blood. The pathological anatomy of these conditions is excellently described in a paper by Wilks [15] on " Sanguineous Meningeal

Effusion (apoplexy) spontaneous and from injury," in which, however, the clinical data are unfortunately meagre. The rupture of an intracranial aneurysm is probably the commonest cause of the clinical picture described.

Before leaving the subject of the symptomatology of subarachnoid hæmorrhage at the base of the brain I must refer to one other point. The relatively large extravasations of blood seen in the fundus of Case 1 were a striking clinical feature. They appeared to be subretinal, and the discovery of semi-coagulated droplets of blood within the arachnoid sheath of the optic nerves post-mortem suggested that those seen in the fundus had found their way from the general lake of extravasation along this path to the nerve head. I was therefore interested to find a similar instance recorded by Sir William Hale White.[16]

His case was that of a labourer aged 21, who had an aneurysm of the right internal carotid just before its termination, presumably of congenital origin, since there was no other evidence of disease.

After an initial seizure with brief recovery he developed the characteristic symptoms of progressive meningeal hæmorrhage.

On examination of the fundi " There was no optic neuritis, nor atrophy, but on the outer side of the right optic disc was a large, prominent, dark brick-red, sub-retinal swelling. This encroached a little on the disc and was four times the size of it. It was thought to be a sub-retinal hæmorrhage."

At the post-mortem " there was a large amount of clot on the under-surface of the brain, which extended to the 4th ventricle and was $\frac{1}{8}$ in. thick in the sub-arachnoid space all down the spine. The hæmorrhage had passed forwards in the sheaths of the optic nerves, which were much distended with blood clot, and ultimately tore its way forwards under the retina."

This is the only clinical observation comparable with my own which I have been able to find in the literature, although distension of the sheaths of the optic nerves with blood has been described in other cases, and examined microscopically by Bramwell [17] and Mott and Stedman.[18]

Apart from actual extravasation of blood beneath the retina in the manner suggested above, the optic discs may appear swollen and congested from increased pressure, as has been noted by several observers.

The following case furnishes an example of intracranial aneurysm due to infective endocarditis. It is included in the present paper because the symptoms were sufficiently clear to permit diagnosis during life,

Case 4.—H. D., male, aged 25, by profession a clerk, was admitted to Addison Ward under Dr. Hurst on June 16, 1921, with the following history :—

With the exception of scarlet fever at the age of 7, he had enjoyed normal health up to the commencement of the illness for which he was admitted.

Five weeks previous to admission he began to complain of intense headaches, chiefly in the frontal region, which were at their worst in the early morning and would clear up towards evening. Two weeks later he experienced numbness of the left leg and left hand. A week after this, while running to catch a train, he had an attack of urgent dyspnœa.

The headaches gradually diminished in frequency and severity, but on Sunday, June 12, as he was sitting down to his dinner, he experienced a sudden intense pain in the right frontal region. With this he became temporarily blind in the right eye, then was dazed for a few minutes, and when he came to his senses found that the left side of his body was paralysed.

On admission to hospital four days later his chief complaint was of headache and pain in the back of the neck. The neck was slightly arched backwards, the head and eyes turned a little to the right. Attempts at bending the neck forward discovered much resistance due to rigidity, and provoked complaint of great pain. The mental condition was normal. There was some dysarthria. Vision in the right eye was poor, and there were also present a left homonymous hemianopia, weakness in upward movement of the right eye, eccentricity of the right pupil, and an incomplete left hemiplegia, and hemianæsthesia of cerebral type.

The temperature was 99·8°, pulse 95, and respiration 28. Definite signs of endocarditis were found, together with an enlarged spleen. There was no doubt, therefore, that the patient had infective endocarditis, and the probability was that his left hemiplegia was due to an embolus of the right middle cerebral artery.

This, however, did not explain the symptoms of which he chiefly complained, namely, intense right frontal headache and pain and stiffness in the back of the neck.

The additional diagnosis was therefore made of an intracranial aneurysm of infective origin situated at the base of the brain. The right frontal headache, temporary blindness of the right eye, weakness of upward movement of the same eye, and eccentricity of the pupil on that side, suggested that this aneurysm was situated in the neighbourhood of the right optic nerve and the third nerve on the same side.

Under observation the patient's symptoms did not alter materially, with the exception that the pain and stiffness in the back of the neck gradually disappeared in the course of three weeks. He still complained at times of right frontal headache.

Low pyrexia continued with gradually increasing pulse rate, and he died suddenly on June 26.

At the autopsy Dr. Ryle found large friable vegetations upon the mitral and aortic valves and a small deposit in the entrance of the first part of the aorta. The spleen was much enlarged and soft with a very large infarct.

Examination of the brain showed :

(1) An aneurysm about equal to a hazel nut in size situated between the tip of the right temporal lobe and the optic chiasma in close proximity to the right optic nerve, and containing semi-organised laminæ of clot.

(2) Extensive softening in the region of the right internal capsule.

Here, as in Case 1, one may divide the symptoms into :

(1) The neighbourhood signs produced by the aneurysm as an intracranial tumour. These were right frontal headache, disturbance of vision in the right eye, and paresis of the right third nerve.

(2) The signs of the disease—infective endocarditis—causing the aneurysm.

(3) The signs of meningeal hæmorrhage caused by leakage from the sac. Although lumbar puncture was not performed at the time when these symptoms were present, they were almost certainly due to such hæmorrhage, which had been completely absorbed during the three months prior to death.

Case 5 did not come to my notice until this paper, as previously written, had already gone to the press. As in Case 3 the patient remains alive so that the diagnosis is as yet unconfirmed, but I believe the diagnosis of intracranial aneurysm to be well-founded, and include the report with the especial object of furnishing a probable example of an aneurysm of congenital origin.

G. F., male, aged 19, was admitted to Guy's under Dr. Hurst on January 16, 1923, in a comatose state.

The following story of previous illness was obtained.

The patient was one of eight healthy children. He had had the usual childish illnesses, and also an operation at the age of three for " twisted stomach." At the age of seven he is said to have had " sunstroke."

He was first admitted to Guy's Hospital under Dr. Beddard on September 8, 1916. Unfortunately the notes, being written during the war period, are very brief.

The history was that on September 4, 1916, he complained of severe pains in the head and back of the neck, and vomited. On admission his temperature was 99·6, pulse 72, respiration 18. His face was flushed and the pupils were dilated. The head was retracted, and Kernig's sign was positive. Lumbar puncture performed on the day of admission gave cerebrospinal fluid which is briefly reported to have contained a few red blood

cells. No other abnormality. By September 11 the temperature was normal. By the 13th the stiffness of the neck was gone, but on the 16th he still complained of frontal headache, which persisted until the 21st, when he was discharged fit.

Thereafter he remained in perfect health until February 6, 1921. He then suddenly felt ill and giddy, and had pains in the frontal region. He was said to have vomited blood and slime about half a dozen times.

He was again admitted to Guy's under Dr. Beddard on February 9, 1921. On admission the temperature was 99·2. He complained of very severe frontal and occipital headache, which was constant and not relieved by removal of the pillow.

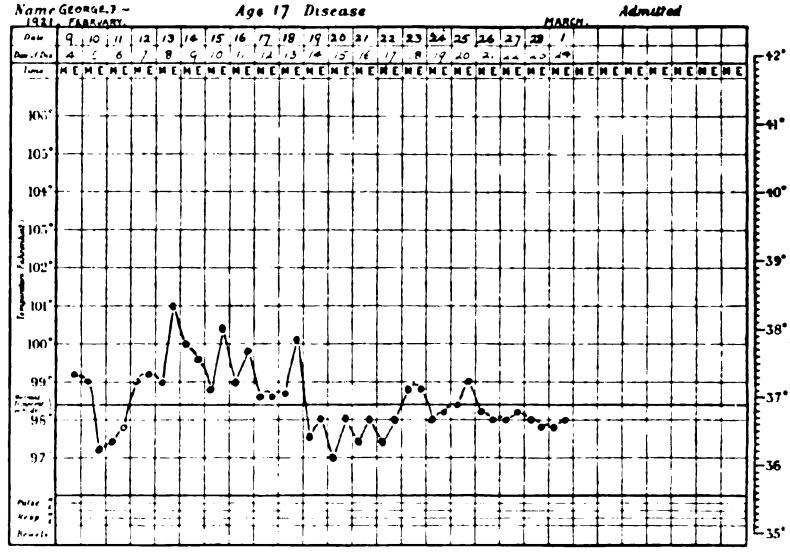

FIG. 3.

Case 5.—Temperature chart during period of second admission.

His pulse was full and strong and of high tension, rate 80 His head was retracted and he could not protract it, having severe pain when trying to do so. The systolic blood pressure was 110; diastolic 89. Tongue dry and furred. Kernig's sign was positive.

Lumbar puncture was performed on February 11 (*i. e.* on the sixth day of his illness). Pinkish, opalescent fluid issued at high tension. Examination of this fluid gave the following results: negative Wassermann reaction, many red cells, and white cells only to correspond to the blood; protein (cells removed) 0·03 per cent.; sugar, normal. Allowing for the blood the fluid is normal.

On February 15 the patient was feeling a good deal better, his headache having almost completely disappeared. The head was still much retracted,

Lumbar puncture was again performed on February 14. The report states that " the fluid contains a considerable number of red cells, and, when freed from cells, has a distinct yellow colour, and shows the hæmoglobin spectrum, showing that some blood is laked, *i. e.* that the blood is apparently old. White cells, about half of which are lymphocytes, are in well-marked excess of the blood and excess of the normal fluid. Sugar, normal; protein, about 0·05 per cent. after removal of the cells."

On February 22 the head retraction was much less. The chin could be protracted to the chest but the movement was accompanied by pain in the back. Kernig's sign was much

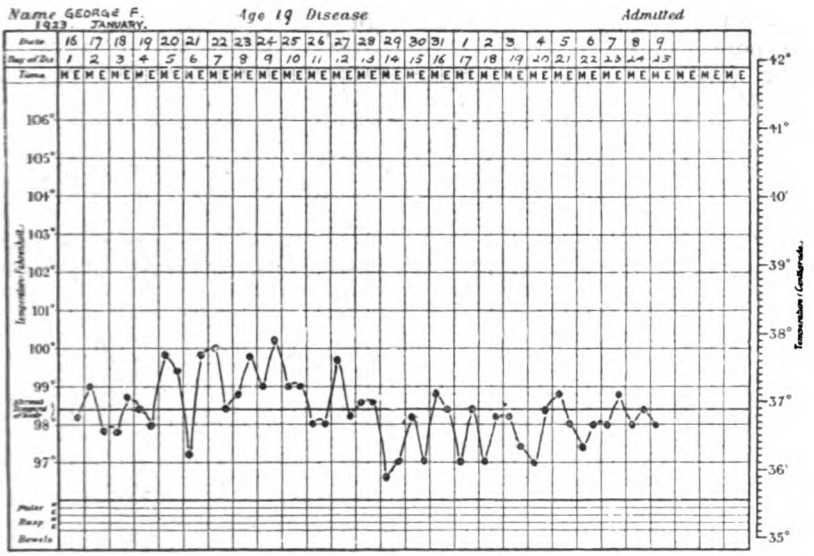

FIG. 4.

Case 5.—Temperature chart during period of third admission.

less marked. He complained of headache only on waking in the morning.

The temperature chart during this period is shown in Fig. 3. The diagnosis suggested was a mild streptococcal meningitis with recovery. Anti-streptococcal serum was administered on February 17 and subsequently the tonsils were removed and an autogenous vaccine given.

He was discharged free from symptoms on April 3, 1921.

When he was admitted for the third time on January 16, 1923, under Dr. Hurst, the history was that he had remained perfectly well since last discharged from hospital, until he awoke on the morning of admission complaining of headache, stiffness of the neck and nausea. He got up at 7.30, had some tea at 7.45, vomited, and collapsed in a condition of coma.

On admission the following observations were made by the clinical assistant, Mr. Graham Bonnalie. There was paresis of the left side with flaccid limbs and absent tendon jerks : slight ptosis on the right : marked retraction of the head and positive Kernig's sign. Both optic discs appeared to be slightly swollen. Lumbar puncture revealed a heavily bloodstained fluid under increased pressure. The fluid was collected in two tubes each of which appeared to contain about the same proportion of blood, and when the specimens were examined an hour later, the corpuscles having settled to the bottom of the tube, the supernatant fluid was definitely tinged with red showing that laking had occurred. The urine contained sugar in considerable quantity. On the following day he was semi-conscious, the tendon jerks were elicitable on the left side, and both plantar responses were extensor. On the 18th the condition was much the same. Urine normal.

When I first saw him on the 19th he was not quite so well, being roused with difficulty. The most marked feature of the case was the picture of meningeal irritation. The head was retracted and the neck stiff. Kernig's sign was definitely present. The optic discs both showed a slight degree of swelling, the left more than the right, and a small retinal hæmorrhage was seen in each fundus. The hemiparesis of the left side persisted with increased tendon jerks and extensor plantar response.

Lumbar puncture was again performed and fluid obtained which appeared to be under slightly increased pressure and contained much altered blood.

From this time forward the boy grew steadily better. On the 26th the swelling of the discs was less and on February 5 they appeared normal. The neck stiffness was slow in disappearing and was still noticeable on February 5, and a slight degree of left hemiparesis with altered reflexes persisted. He complained at times of frontal headache, but his mental condition was clear and he was anxious to be allowed up.

The temperature chart from the date of admission up to February 9 is shown in Fig. 4.

The records of this case show that on three occasions during the past seven years the patient has been admitted to Guy's Hospital with the symptoms and signs of acute meningeal irritation from which he has rapidly recovered. On each occasion blood has been found in the cerebrospinal fluid, which has been in all other respects normal. On the last occasion it was particularly noted that the blood was evenly mixed with the fluid and was already laked. The occurrence, during the last attack, of transient papillœdema, and the signs of a lesion of the right crus cerebri (paresis of the right third nerve with left hemiparesis) complete the story, which is entirely in accord with the diagnosis of intracranial aneurysm, probably at the point of junction of

the right internal carotid and middle cerebral arteries. The absence of signs pointing to any other pathology, and the age of the patient favour a congenital origin.

The occurrence of long intervals of freedom from symptoms between the attacks in this case is of considerable interest. As a feature of intracranial aneurysms, especially the congenital variety, this point has been well recognised by the German authorities, whose experience is summarised by Wichern.[3] It is none the less difficult to understand the conditions which determine fresh leakage, after a lapse of 5 years.

A comparison of the temperature charts from Case 3 (Fig. 2) and from Case 5 in the second and third attacks (Figs. 3 and 4) shows considerable similarity. In neither of these two cases has the diagnosis as yet been confirmed by autopsy, so that it would be rash at the moment to assert that such a temperature chart is a characteristic feature of leakage from an intracranial aneurysm. But the occurrence of fever under such circumstances should not surprise us, in view of the pyrexia which not uncommonly attends the simple effusion of blood into other serous cavities. As an instance may be cited the fever observed in cases of sterile hæmothorax following concussion of the chest wall.

Of the other cases of the present series, in Case 1 a temperature of 99·8 was noted on admission. In Case 2 no record of the temperature was made, and in Case 4 the co-existence of infective endocarditis renders the chart of little value in this connection. In the first attack for which Case 5 was admitted the temperature was 99·6 on admission (being the fifth day of illness) and came down to normal on the eleventh day of the illness.

Summary and Conclusions

1. Five cases are related in which the diagnosis of intracranial aneurysm was made before death.

In two of these cases the diagnosis was confirmed absolutely at autopsy; in one other the post-mortem was not complete; meningeal hæmorrhage was discovered at the base of the brain and an aneurysm was thought to be present: the remaining two patients are still alive.

2. The signs met with in cases of intracranial aneurysm may be divided into (*a*) neighbourhood signs, (*b*) signs of the disease (if any) causing the aneurysm, (*c*) signs of leakage from the sac.

3. Leakage of blood into the sub-arachnoid space at the base of the brain gives rise to clinical signs upon which the diagnosis of this occurrence may be made with reasonable

certainty. This diagnosis may be confirmed by means of lumbar puncture.

4. The conjunction of the history of such an attack of basal meningeal hæmorrhage with the signs of a tumour at the base of the brain is sufficient evidence for the diagnosis of intracranial aneurysm.

5. The diagnosis of intracranial aneurysm should be considered when the signs of an intracranial tumour at the base of the brain are associated with those of cerebral arteriosclerosis or infective endocarditis.

My thanks are due to Dr. Hurst for allowing me access to Cases 4 and 5, to Dr. F. H. Thomson of the North Eastern Hospital for permission to publish the notes of Case 3, and especially to Professor Harvey Cushing whose enthusiasm originally inspired these observations.

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CONTRIBUTIONS TO THE CLINICAL STUDY OF INTRACRANIAL ANEURYSMS

II

By HARVEY CUSHING, M.D., Professor of Surgery, Harvard University.

As Dr. Symonds and others before him have pointed out, intracranial aneurysms of the sacculated variety are far less rare than is commonly supposed, though it is most unusual for the clinician at the bedside even to suggest the possibility of such a diagnosis. That he correctly interpreted the syndrome in the first of the cases included in his paper, whereas aneurysm had not even been considered by others who had examined the patient, the author modestly conceals. The lesson was such an important one to others that at my solicitation Dr. Symonds agreed to report the case.

How it is that a surgeon comes to write a note upon a lesion having such remote surgical bearings may be told. On an average, some thirty patients each month are admitted to the surgical wards of the Brigham Hospital for symptoms which have suggested to their attending physicians the probability or possibility of an intracranial tumour. The cases fall into two groups—the undoubted tumours and the tumour "suspects." The former, which naturally represent by far the larger number, are subsequently subdivided after operation into the verified and unverified tumours. These do not here concern us.

The tumour "suspects" constitute a group of cases of unusual clinical interest and importance, and often present problems of the greatest diagnostic difficulty, including, as they do, various forms both of functional and organic disease—chronic arachnoiditis, encephalitis, arteriosclerosis, nephritis, syphilis, tuberculosis, epilepsy, cephalalgia, and so on, together with a great variety of ophthalmological disorders. It was to this group of cases that Dr. Symonds, during a sojourn of some weeks in the clinic, devoted his particular attention.

The entire tumour series numbers at the present time 826 histologically verified tumours, 454 unverified ones, and possibly an equal number of cases at one time or another under the suspicion of harbouring tumour. Among these are recorded

four proven examples of sacculated aneurysm, all of them having originated near the bifurcation of the internal carotid into the anterior cerebral and anterior communicating vessels. The histories of these cases may be briefly summarised.

No. 1.—This was a patient with a pituitary adenoma (Case No. XV in my monograph on *The Pituitary Body and its Disorders*) in which an aneurysm of the internal carotid was an unexpected post-mortem finding. The history so far as the aneurysmal symptoms are concerned is imperfect. There was a defect in the field of vision on the side of the lesion and the patient's death had occurred without rupture of the aneurysm.

No. 2.—A physician's wife, 52 years of age, was referred to the clinic February 8, 1916, with the presumptive diagnosis of a pituitary tumour, after four months of " eyestrain and disturbance of vision." She had a central scotoma and complained of an ache and pain in the right side of the neck which had come on at the time when her loss of vision was first noticed. She was otherwise without symptoms. The posterior clinoid processes showed some rarefaction, and without admission to the hospital she was referred back to her physician as a pituitary tumour " suspect," not justifying operation.

During the next few months her loss of vision progressed. Despite the absence of a choked disc a diagnosis of right frontal tumour was made, and an exploration was performed by a surgeon in New York, who disclosed what was mistaken for a glioma of the lower part of the frontal lobe. Some months after recovering from this operation, and while still in very good health, she had a sudden " stroke " with coma and death. Autopsy disclosed a ruptured aneurysm the size of a hazel-nut. This arose from the internal carotid and had compressed the chiasm.

These two cases, then, are ones in which an unsuspected aneurysm had caused pressure against the optic chiasm and obscurely suggested a tumour in this locality. They gave none of those symptoms of an intracranial aneurysm to which Dr. Symonds draws attention—symptoms which in reality are those indicating the rupture of an aneurysm.

In the following case these indications were sufficiently clear, but even so the diagnosis was not even suggested.

No. 3. Surgical No. 6433.*—An Irish servant girl, aged 26, was admitted March 15, 1917. Seven weeks before entrance there was a sudden onset of pain in the right side of head, neck, shoulder, arm and hand, followed in a few hours by diplopia, right ptosis, and numbness of the right brow and cheek. Of late, occasional attacks of vomiting and vertigo with continuous discomfort in back of head and neck, and lowered vision.

* Case reported by Henry Viets as " Unilateral ophthalmoplegia." *Journal Nerv. and Ment. Dis.*, April 1918.

The positive findings on examination were a complete right ophthalmoplegia with ptosis and immobile pupil; hypæsthesia of the right trigeminal, supra-, and infraorbital skin fields; systolic blood pressure 200. The urine was negative, likewise the Wassermann reactions. A lumbar puncture had been made shortly before admission, which according to report showed thirty cells but no blood. X-ray negative. Visual fields and vision normal.

Of the five examiners in the case no one suggested aneurysm. A meningioma of the trigeminal sheath was suspected, and an exploration was made in the subtemporal region. On incising the dura low down in the fossa, the wall of a pulsating aneurysm was disclosed.

She was discharged unrelieved, and died suddenly a year later; no autopsy.

No. 4. Surgical No. 13,075.—This is the case forming the basis of Dr. Symonds's report—one in which the final and fatal extravasation from rupture occurred while the patient was in the hospital.

The only other verified cases in our clinical and pathological records are two which occurred in the service of my colleague, Dr. Christian, with whose permission I may make this note of them. They were both examples of recent rupture with fatality, and the diagnoses were not made until after death. One of them has already been reported.*

No. 5. Medical No. 5430.—A negress, aged 32. Her acute intracranial symptoms, suggesting apoplexy, had been of sudden onset while at work the same morning. She entered the hospital *in extremis* and died six hours later, having acquired a divergent squint during this interval. The systolic blood pressure rose from 180 to over 300, when it could no longer be registered. The pulse was slow. A lumbar puncture gave bloody fluid. Ophthalmoscopic examination showed an extensive fresh hæmorrhage covering the disc and retinæ, and it was on this basis that the case was reported. The autopsy revealed general arteriosclerosis and a pea-sized aneurysm of the left internal carotid, which had ruptured.

No. 6. Medical No. 12,604.—A man of 36 whose symptoms, chiefly of occipital pain, began twelve days before entrance. He seemed to be recovering, when, on the day before admission, he suddenly became worse and had a convulsion. On admission he was irrational, showed cervical rigidity, and had fever. No oculomotor paralyses were recorded, but there was blurring of the right disc. A diagnosis of meningitis was made. Successive

* Doubler, F. D., and Marlow, S. B.: a case of hæmorrhage into the optic-nerve sheaths as a direct extension from a diffuse intrameningeal hæmorrhage, caused by rupture of aneurysm of a cerebral artery. *Arch. Ophth.*, 1917, xlvi., No. 6, 533–536.

lumbar punctures showed bloody spinal fluid. Wassermann negative. Death five days after admission. Autopsy: a ruptured pea-sized aneurysm at the junction of the right carotid and anterior cerebral arteries. No cerebral arteriosclerosis.

Here then were four examples of the intracranial rupture of a bifurcation aneurysm of the internal carotid disclosed at autopsy, only one of which was diagnosed before death. Probably all of them should have been recognised.

The review of these cases under the stimulus of Dr. Symonds's paper has led me to feel that many other patients must have passed through the clinic with an unrecognised aneurysm who had temporarily recovered from the first symptoms produced by a pinpoint rupture. A cursory search reveals four of them, each with a typical history, masquerading under the following diagnoses—hæmorrhagic pachymeningitis, ophthalmoplegia externa, ophthalmoplegic migraine, tumour suspect of trigeminal nerve sheath. A more diligent search would probably bring more of them to light.

If my present interpretation of these records is to be relied upon and the cases really represent the rupture of an aneurysm, the condition shows a marked degree of spontaneous recoverability. The following is an example—the case having been diagnosed as ophthalmoplegic migraine (basilar syphilis?).

Surg. No. 3665.—A meat-cutter, aged 54, entered the hospital October 7, 1915. An acute onset of symptoms a month before entrance with severe right-sided cephalalgia and vomiting, followed four days later by ptosis and ophthalmoplegia. He largely recovered from this attack, but two days before entrance he had a similar "stroke," leaving him with impaired vision.

Examination showed a complete right-sided external ophthalmoplegia with ptosis and immobile pupil. No trigeminal symptoms observed. Extensive bilateral hæmorrhages in both eyes. A bloody cerebrospinal fluid. Impairment of hearing. Wassermann negative. Systolic blood pressure 205. General arteriosclerosis.

During his hospital sojourn the paralysis began to disappear. He was discharged, and two years later reported himself well except for occipital headaches.

Certainly, in view of Dr. Symonds's report, an aneurysm should always be considered in a differential diagnosis when an apoplectic attack or a series of attacks of comparatively sudden onset is followed by symptoms pointing to the region of the internal carotid in its intracranial portion, namely, a unilateral oculomotor palsy with ptosis, and occipito-frontal pain with lowered sensitivity of the upper trigeminal skin field. Should

there be in addition subhyaloid retinal hæmorrhages, and should the cerebrospinal spaces be found to contain free blood (or possibly even xanthochromia in the intervals between periods of leakage), a diagnosis, as the author makes clear, is reasonably certain. Moreover, hypertension and arteriosclerosis need not characterise the clinical picture, for many of these lesions occur in comparative youth and are unquestionably mycotic in origin, the point of bifurcation of an arterial trunk under these circumstances being the spot most amenable to injury with subsequent weakening of the arterial wall.

Were sacculated aneurysms before rupture prone to give neighbourhood-symptoms indicative of their pressure, they certainly would have been exposed more often during the course of the many exploratory operations which have been performed for tumours in the parachiasmal region. At a recent meeting of a newly organised society composed of neurological surgeons, an inquiry was made as to how many of the members had encountered sacculated aneurysms in the course of their intracranial operations. One of them had done so during an exploration for a presumed tumour adjacent to the sella. Another related a disastrous experience with a lumbar puncture in a patient under suspicion of harbouring a subtentorial growth. About two c.c. of clear fluid had been removed when suddenly fresh arterial blood spurted from the needle. The patient died shortly after. The autopsy disclosed a sacculated aneurysm of the lateral recess which evidently had ruptured at the time of the puncture.

Obviously the neuro-surgeon is not likely unexpectedly to encounter one of these aneurysms, for they rarely produce symptoms until there has been leakage, and the aneurysmal sac itself rarely reaches a sufficient size before rupture (as in patient No. 2) to give symptomatic evidences of its presence. When rupture occurs and the true condition is recognised, whether there are surgical indications such as ligation of the internal carotid, further experience alone can tell.

The diagnosis of these cases during life must depend upon that form of clinical acumen, based on a thorough knowledge of normal and pathological anatomy, which has distinguished so many English clinicians, both physicians and surgeons—men of the type of the Coopers, Bright, Addison, Hodgkin and Gull, whose names have made Guy's Hospital famous.

STUDIES ON TUMOUR FORMATION

By G. W. NICHOLSON, M.D., Lecturer in Morbid Histology, Guy's Hospital.

VI. THE HYPERNEPHROMATA, OR STRUMÆ SUPRARENALES ABERRATÆ

No review of the tumours that arise, or are said to arise, in congenital malformations and displacements can claim to be complete without an examination of the so-called "Hypernephromata" of the kidneys and of certain other parts of the body. They were, at one time, universally believed to afford the strongest proof of the correctness of Cohnheim's theory. Lubarsch [21] made the statement in 1910 that all malignant epithelial tumours of the kidneys, with the exception of those of the pelvis, arise in accessory suprarenals. It was not until quite recently that this view, originally brought forward by Grawitz [15] in 1883, has begun to fall into disfavour, and that more than an occasional paper advocating the renal origin of the hypernephromata has appeared. The subject is of sufficient interest and importance to excuse an historical review of some of these, especially since it is one of the few dealing with morbid histology in which English writers have taken an active part.

Before attempting such a review it will be necessary briefly to describe the structure of the hypernephromata. Since I cannot improve upon Dr. Kettle's [18] description, I have taken the liberty to copy it verbatim.

"The naked-eye appearance of a hypernephroma is very characteristic, and renders it possible to make a diagnosis from a macroscopic examination in a high proportion of cases.

"In typical examples there is a primary encapsuled tumour surrounded by daughter tumours, which diminish in size as the limits of the growth are approached. Unaltered areas of tumour tissue are of a yellowish colour, but the cut surface has usually a mottled, deeply hæmorrhagic appearance, for the growths are exceedingly vascular, and there is nearly always an extensive extravasation of blood. Central cystic degeneration of the larger nodules may occur, but more commonly there are areas of mucoid degeneration mingled with zones of dense fibrosis, the

appearance as a whole suggesting very strongly the presence of cartilage.

"The *microscopic* structure is of great interest. The tumour cells are cuboidal in shape, but they are liable to become distorted as the result of mutual pressure; sometimes they are distinctly columnar. They have a small, round, deeply staining nucleus, and are distinguished by the clear, vacuolated appearance of their cytoplasm, an appearance due partly to hydropic distension, partly to the solution, in the process of preparation, of the fat and glycogen present in the fresh state. Their arrangement is extremely variable.

"Trabeculæ or solid alveoli are common, and the latter may exhibit a lumen from the degeneration of the central cells. In some tumours there is a true acinous formation, and in

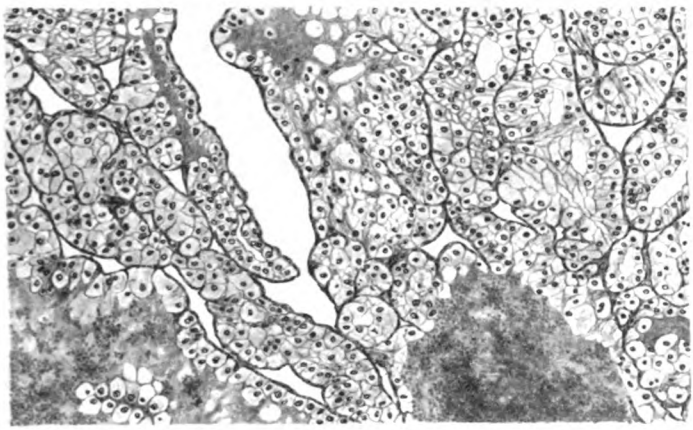

FIG. 54.

Hypernephroma of kidney. Magnif. 115.

others the cells are often disposed in a papillomatous manner around a vascularised connective tissue core. Occasionally cystic spaces, which may be partly filled up by an ingrowth of the lining cells, are formed, and every now and again the cells may be loaded with pigment granules, probably as the result of old hæmorrhages.

"Except in the older parts of the tumour the stroma is always extremely scanty, and the groups of cells are separated by, and rest upon, delicate capillaries which consist of little more than tubes of epithelium. The vascular supply is always abundant, and the capillaries are often dilated into large sinusoids."

Most of these appearances, with the exception of true acini, are to be seen in Fig. 54, taken from a typical hypernephroma of the kidney.

PART I

Grawitz,[15] in 1883, separated certain relatively common tumours from the rare true lipomata of the kidneys, with which they had until then been confounded. He examined a series of small sub-capsular nodules of these organs, together with two large neoplasms, one of which had formed metastases in the lymph-glands and the lungs, and suggested that they arise in emigrant suprarenal tissue. He therefore named them *strumæ suprarenales aberratæ*. The arguments by which he supports his theory are the following: (1) The position of these tumours in the cortex, close under the renal capsule, where displaced suprarenal tissue is not uncommonly met with. (2) The structure and shape of their epithelial cells. They differ radically from those of the renal tubules, but are strikingly similar to those of the suprarenals. (3) The fat contents of the epithelial cells, in the form of large globules. Renal epithelium does not undergo an infiltration with fat (as against a fatty degeneration): but this occurs regularly in the suprarenal cortex. (4) The presence of a capsule around the tumours. (5) The relation of the epithelium to the stroma. Near the periphery its cells form irregular rows, corresponding with the structure of the suprarenal cortex, whereas near the centre they lie in small groups, as in the medulla of that organ.* Grawitz compares his tumours with two adenomata of the suprarenal cortex, and concludes that their structure is identical.†

In the following year Grawitz [16] returned to this subject. He recapitulates his former arguments, points out the frequency with which accessory suprarenals and hypernephromata are found under the capsule of the kidneys, and shows that the latter occur even at some distance below the surface in the inter-rencular septa.‡ He divides the tumours of the kidneys into papillary and alveolar forms. He is prepared to claim an origin from suprarenal tissue for the latter only. The papillary

* Grawitz and some of the earlier writers believed that hypernephromata contain suprarenal medulla in addition to cortex. But this view was abandoned when the dual origin of these tissues was generally accepted, and the reaction of the cells of the medulla to chromates became known. In the following pages the origin of these tumours from the cortex need therefore be alone discussed.

† In one of his cases Grawitz found extensive amyloid changes in the vessels of the renal tumour and in those of the suprarenals, whereas those of the kidneys were free, with the exception of the glomerular tufts, which were but slightly affected. On this he bases his sixth argument. It need not detain us, since the presence of amyloid in the vessels of two tissues cannot reasonably be brought forward as a proof of their identity.

‡ But his drawing (Plate VI, Fig. 4) shows the tumour at the deep end of a fibrous band which can equally well be interpreted as a scar, nor is his description incompatible with this interpretation.

forms differ too radically from them for it to be possible to assume an identical matrix for both forms. They arise in the renal epithelium.* Grawitz makes the following admission: "I will not dispute the fact that adenomatous and papillary proliferations of glomeruli and of renal tubules occasionally take place at the periphery of such strumæ; that the disturbance can therefore have implicated the earliest protophase of the kidney substance itself."

The first to cast a doubt upon the suprarenal origin of the hypernephromata of the kidneys was Sudeck,[31] in 1893. He maintains that these tumours are always tubular in type, and that they are true renal adenomata. Because their capillaries are surrounded by little or no areolar tissue circulatory disturbances are exceedingly common in them, resulting in hyaline and fatty degeneration of the epithelium, whose cells become swollen and distorted. The lumina are thus obliterated. When, however, a small hæmorrhage takes place into an obliterated tubule, its condition approximates to that of the tubules of the kidneys, since the absent internal pressure is replaced, and its epithelium now forms a single layer of cubical cells. The papillary forms are nothing more than cystic tubular specimens. The papillæ are never true and do not end in a free point, since they never contain more than one capillary, and an efferent, as well as an afferent vessel must be present in a true papilla. In serial sections they can invariably be shown to be complete septa. Sudeck describes transitions between the cells of a large malignant hypernephroma and those of the neighbouring hyperplastic renal tubules, and believes that they prove the renal origin of the tumour.† He discusses the small adenomata of granular kidneys as something quite different from the adenomata referred to above, and concludes that they are not true tumours, but hyperplasias of renal tubules, caused by inflammatory proliferation of their epithelium. He cannot deny that they may give rise to true adenomata, although he does not favour this view.‡

In the same year Driessen [9] wrote a paper on endotheliomata rich in glycogen. He describes a pulsating tumour of the ulna, whose cells are markedly epithelial in type, loaded with glycogen

* Grawitz is by no means clear on this point. In his first paper he states that the urine of one of his cases contained villous masses of new growth, without, however, making use of this observation in his argument. In his second paper he refers to this case as a true hypernephroma of suprarenal origin, and ascribes the villi to softening and disintegration of the tumour.

† I have discussed these spurious transitions in Study V, and need not do so again. It is obvious from Sudeck's descriptions and drawings that he was misled by them.

‡ It is a suggestive fact that all his specimens were found in granular kidneys.

and fat, and presenting a characteristic perivascular arrangement. In places these cells are smaller; here they bear a close resemblance to plasma-cells. They appear to have originated in the endothelium of lymph-spaces, since it is impossible to deny the presence of transitions between them. The tumour is therefore an endothelioma. He compares it with two renal neoplasms, whose structure is practically identical with it, and concludes that these too are endotheliomata, and not *strumæ suprarenales aberratæ*. The general application of Grawitz's theory to nearly all tumours of the kidneys is inadmissible, although it is no doubt correct in individual cases. Although Driessen's renal neoplasms possess all the structural characters of the hypernephromata, these are all shared equally by the tumour of the ulna. It would be going too far to assume that the latter has originated in a suprarenal rest that has emigrated into a bone. Since he has shown that this tumour is an endothelioma, those of the kidneys are endotheliomata as well.*

In the following year Lubarsch [20] wrote a defence of Grawitz [15] and a criticism of Sudeck [31] and Driessen.[9] He discusses the morphological characters and staining reactions of the hypernephromata, and points out their correspondence in these respects, as well as in the occurrence of giant-cells, early and free invasion of veins,† the structure of the capsule, and the presence of fat and glycogen, with the suprarenals and the neoplasms that arise in them. He devotes a considerable amount of space to an investigation of glycogen, and concludes that this substance (or, more correctly, these substances) is an essential constituent of the hypernephromata of the kidneys and of the tumours of the suprarenals, and that it is of great diagnostic importance. Tumours that originate in embryonic cell-rests are peculiarly rich in glycogen.‡ The rest of Lubarsch's paper is devoted to a criticism of Sudeck [31] and Driessen.[9] His arguments against the former are: (1) True cysts never occur in hypernephromata, and the branched "villous" septa are of no diagnostic importance. (2) The shape of its cells is no criterion of the origin of a tumour. Cylindrical cells are, however, found in the suprarenals of man. Rarely they even line spaces. These are much more evident in accessory suprarenals that are on the point of becoming hyperplastic. (3) Sudeck's [31]

* Driessen is not alone in this assumption. It would indeed have been strange if aberrant tumours like the hypernephromata had escaped this fate. One is reminded of the time-honoured argument: "Men are bipeds, birds are bipeds. Therefore men are birds."

† Manasse [22] has shown that the vessels of adenomata of the suprarenals, as well as those of the normal gland,[23] frequently contain epithelial emboli.

‡ We now know that rapidly growing tumours very generally contain a large amount of glycogen.

transitions between the cells of the hypernephroma and those of the renal tubules are spurious. (4) The structure of the hyperplasias of an organ always corresponds very closely indeed with that of its adenomata. This rule applies universally. Since Sudeck [31] admits that the "adenomata" of granular kidneys are hyperplasias, and that they are totally different from his so-called true adenomata, he has himself brought forward the strongest proof of how radically the latter differ from adenomata of undoubted renal origin.* Against Driessen [9] he argues that it is wrong to assume that, since the structure of renal hypernephromata and of certain tumours of bones (which certainly do not originate in suprarenal tissue) is identical, the ætiology of the two must necessarily be the same, and that the former therefore cannot arise in accessory suprarenals. He takes the view † that, if accessory suprarenals were unknown in the kidneys, it would be inadmissible to derive the hypernephromata from suprarenal tissue. If these displacements had been shown to occur in the bones, there would be no objection to the assumption that Driessen's [9] tumours are hypernephromata.‡

The late Mr. Targett [33] made the following statement in 1896: "During the past five years I have examined a very large number of renal tumours of various kinds, and I feel certain that the specimen here recorded is the only one in my experience which has presented the features of an adrenal tumour. Hence, while thoroughly accepting the hypothesis of Grawitz as to their origin, I believe that the frequency of this class of tumour has been much exaggerated by some writers." §

The next to investigate the question was Ricker,[27] in 1897. He divides the tumours of the kidneys into two groups. Both of these are sub-capsular. The members of one group, which is relatively rare, are solitary. They consist of solid columns of polygonal epithelial cells, which usually contain a large amount of fat. There is a tendency to the formation of multinucleated giant-cells. The epithelium typically abuts directly upon the capillaries, but is sometimes separated from them by a small amount of connective tissue. The essential characteristic of the tumours of this group is their solid structure. Secondary

* But the real question is not: What did Sudeck believe to be true? but: What is the actual truth?

† One from which many followers of Cohnheim have departed to the great detriment of pathology (*vide infra* Pick,[26] Wilson and Willis [37]).

‡ No useful purpose would be served by pursuing the controversy that now arose, and in which several pathologists took part. Suffice it to say that Sudeck [32] abode by his opinion, but did not convince others.

§ This is the first warning in the English language that I know of against the blind acceptance of Grawitz's views. It is a significant fact that it should have been uttered by our greatest histologist.

spaces and cavities are, however, produced with great frequency even in small specimens, by disintegration of the central cells of the columns. These solid tumours originate in displaced suprarenal tissue; they are the true hypernephromata. The other group is much commoner. It consists of true tubular or cystic tumours. These are frequently multiple. Their spaces and cysts are traversed by trabeculæ which, in the actively growing peripheral parts, contain an often considerable amount of connective tissue in addition to capillaries. The former disappears in the older central parts of the tumours, so that here the epithelium rests directly upon the capillary endothelium. The epithelium is cylindrical and often very tall, its cells are club-shaped. They are vacuolated by the presence of numerous droplets of fat. These tumours are true renal adenomata. Ricker shows that they arise in the fibrous scars of old infarcts and arterio-sclerotic patches, in the fibroses of chronic nephritis, as well as occasionally in apparently normal kidneys. Large, fully developed and malignant specimens of these two groups are indistinguishable from each other. Closely related to the tumours of the second group, early stages of which some of them no doubt represent, are the solitary small cysts of healthy kidneys. Their epithelium consists of a single layer of very tall, club-shaped, cylindrical cells, honeycombed with globules of fat.* There is no evidence of an inflammatory reaction in their neighbourhood. Ricker found one of these cysts in a child of 8, and suggests the possibility of a congenital origin for them.†

Although Ricker [27] was the first to prove that the epithelium of renal tubules undergoes fatty changes identical with those found in the hypernephromata, the significance of this fact was overlooked, and every year the percentage of tumours of the kidneys said to originate in accessory suprarenals increased.

None of the papers that appeared during the next few years need be mentioned, with the exception of that of Pick,[26] of the year 1901. It deals with a hypernephroma of the ovary in particular, and with *strumæ suprarenales aberratæ* and accessory

* Grawitz's [15] statement, that fatty infiltration of renal epithelium apart from necrosis does not occur, is thus refuted.

† There is no reason why the epithelium of a cyst like those in Fig. 12 (II.) should not proliferate when irritated by retained secretion or from some other cause, precisely in the same way as the other epithelia of the body. Should the irritant act and proliferation take place before birth, a truly congenital tumour may even result. Adenomatous growths are sometimes found in congenital cystic kidneys (*vide* Fig. 10 (I.)). It is even conceivable that renal cysts within the suprarenals (cf. Fig. 24 (III.)) give rise to tumour formation, and that, as was suggested by Ricker in an earlier part of his paper, true renal neoplasms may occur in these organs.

suprarenals in general, and raises questions of primary pathological importance. Pick discusses the so-called hypernephromata of bones. He believes that, even when no renal or suprarenal tumour is found post mortem in such cases, there is nevertheless a connection between the neoplasm and the suprarenal glands. He argues that a chorion-epithelioma occasionally originates outside the uterus in a chorionic villus that has been carried away by the blood stream, without the presence of malignant changes in the placenta, and that a normal thyroid has been known to give rise to metastases. There is no reason why the suprarenals should not be capable of a similar dissemination, since they, as well as the thyroid, are ductless glands, whose secretion enters the blood directly, and whose epithelium is therefore in intimate contact with the blood vessels. He refers to Manasse's [23] discovery of emboli of suprarenal cells in the veins of the normal organ, and points out that these glands and the thyroid are eminently capable of regeneration, and that their tumours frequently give rise to metastases in the bones. Far from upsetting Grawitz's theory of the origin of the hypernephromata, these tumours of bone confirm it, since they are themselves true hypernephromata, and have arisen in emboli of suprarenal cells in the bones.*

* I am not prepared to discuss the ectopic chorion-epitheliomata fully just now. The emboli of chorionic villi that are commonly met with in pregnancies never show signs of growth, but are always in a more or less degenerate condition. In spite of the number of cases recorded I cannot avoid the impression that the placenta must have been in some way abnormal. The case of the thyroid is similar. In Study I. (p. 243) I referred to v. Eiselsberg's [11] colloid goitre with a functionating metastasis in the sternum. Very similar cases have been recorded in which the thyroid was not even enlarged. The most striking fact about v. Eiselsberg's case is the one that the tumour of the sternum grew slowly at first and rapidly later. The scapular tumour that developed after its removal had no influence on the course of the myxœdema. The case proves clearly that cells of the thyroid that do not form part of a carcinoma and therefore are not what we commonly call "malignant" occasionally enter the blood stream and are carried away to the bones, where they lodge. But it teaches us more than this; it suggests that the ultimate fate of a thyroid embolus depends upon the state of the thyroid gland itself. The embolus grows if the gland is insufficient, since it now performs a useful function. Although there is absolutely no reason to doubt the correctness of the histological diagnosis in cases of metastasis of thyroid tissue without enlargement of the gland, it remains to be seen if there were no signs of thyroid insufficieney after removal of the secondary tumour, and if the claim that the thyroid was physiologically normal can be upheld. Pick makes no mention of this point. Again, the fact that the sternal tumour in v. Eiselsberg's case grew slowly at first indicates that it consisted of non-blastomatous thyroid tissue, which was capable of performing all its physiological functions. It was removed because of late it had increased rapidly in size; it was now found to be a carcinoma with small globules of colloid. Does not this suggest that, coincidently with its recently accelerated rate of growth, its structure was becoming more and more atypical or anaplastic, and its functions more and more imperfect in consequence? Had it not been removed, would not symptoms of myxœdema shortly have supervened? The structure of the suprarenals and thyroid is such that there is no reason why some of their cells should not frequently be carried away by the blood. But Pick does not even raise the question if it is

The appearance of Stoerk's [30] paper in 1908 marks an epoch in the history of the hypernephromata. He begins by asking two questions: Why are the hypernephromata invariably found in the kidneys and never in the suprarenals? Why do the tumours of the latter, be they innocent or malignant, always differ radically from them? If the hypernephromata originate in accessory suprarenal tissue we should, on Cohnheim's theory, expect them to be commonest in the suprarenals themselves, since small accessory nodules abound in and immediately around these glands. But a typical case has never yet been described in this situation.* The distribution of the hypernephromata in the kidneys does not correspond with that of the accessory suprarenals in these organs. No hypernephroma has ever been seen within the layers of the renal capsule, unconnected with the tissues of the kidney, whereas accessory suprarenals are not uncommon here.† Although the grouping of the cells of hypernephromata is very similar to that of those of the suprarenal cortex, their structure bears no morphological resemblance whatever to them. They are degenerate forms of the small protoplasmic deeply staining cells often found in these tumours. Their glassy, swollen appearance is caused by hydropic changes, which are invariably absent in the suprarenals. In addition, they generally contain numerous globules of fat, part of which (and often the greater part) is doubly refracting to polarised light. This substance is typical of the renal epithelium in certain diseases of the kidneys, and occurs commonly in a variety of tumours in many parts of the body. There is some

necessary or not for these cells to perform a physiological function in order to survive and multiply. Is not this the only respect in which non-blastomatous cells differ from those that are blastomatous? I can see no reason why suprarenal cells should not be carried to the bones (or why they should not occasionally even give rise to a tumour in this situation), but I very much doubt if they ever proliferate in their new surroundings as long as the suprarenals are healthy. At any rate, I agree with Lubarsch [20] that it is quite unjustifiable to claim that a tumour of bone is a true hypernephroma until the presence of typical accessory suprarenals shall have been demonstrated in the skeleton. This has never been done to my knowledge.

* Stoerk declares that, should a hypernephroma of the suprarenals be recorded, he would explain it as a case of tumour formation in displaced renal tubules (*vide supra*, footnote to Ricker's [27] paper).

† I have, however, seen a small intra-capsular cystic papilloma, surrounded by dilated tubules, whose renal origin there is no reason to doubt. These structures are separated from the surface of the kidney by the deepest layers of its capsule. Fig. 55 shows a part of it. Unfortunately I did not discover it until after I had stripped the capsule. A fragment of kidney is, however, still adherent to it on the right of the drawing. Whether the tubules were isolated during development or as the result of a scar or patch of cirrhosis I do not pretend to know. In the latter case they would constitute an "acquired tissue malformation" (Study IV.). At all events, the specimen teaches us that an intra-capsular hypernephroma, should one be found, is not incompatible with Stoerk's arguments. Both kidneys were granular and contained numerous adenomata and hyperplastic tubules. One of the latter is illustrated in Fig. 34 (IV.).

evidence that the chemical composition of the corresponding substance in the suprarenals is different. Stoerk divides the hypernephromata into solid alveolar and tubulo-perivascular forms. They are all variants of an essentially tubular structure. The hyaline casts contained within their alveoli are probably the result of secretory activity of the epithelium. Under the influence of factors that loosen the cohesion of the cells typical villi make their appearance. In order that they should be produced a free surface is necessary from which, and a space into which, proliferation can take place. In spite of statements to the contrary, tubules and cysts never occur in the suprarenals of man. The alveolar forms of the hypernephromata are

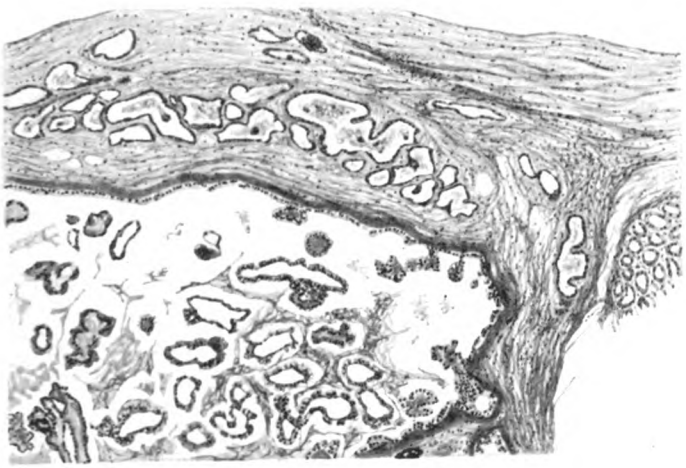

FIG. 55.

Adenoma of capsule of kidney, surrounded by tubules. Magnif. 50.

connected with the small pale nodules frequently found on the surface of granular kidneys by numerous intermediate stages. These consist of solid strands and buds of renal epithelium which may, however, acquire lumina and contain hyaline casts. They are the result of regenerative hyperplasia. Their cells are hydropic and fatty, and are multinucleated occasionally. Some of these structures functionate more or less perfectly, no doubt; others proliferate as small tumours, that possess all the structural characters of, and indeed actually are, hypernephromata of the alveolar type in miniature. Every cyst of the kidneys can give rise to villous formations, usually associated with hydropic swelling and hyaline and fatty changes of its epithelium. Stoerk traces the papillary adenomata to these cysts, and points out that they increase in frequency as life

advances, in proportion to the increase of granular changes in the kidneys. The papillary carcinomata form one more link in the chain. Their structure is exceedingly variable, one segment presenting a villous appearance and another that of a typical hypernephroma. The evidence is sufficient for the following series to be set up: Sclerosis of the kidneys,—cysts,—papillary cystic adenomata,—hypernephromata. Stoerk does not deny the possibility of the origin of tumours of the kidneys in accessory suprarenals, but has not seen an instance of this. His conclusions are: (1) Tumours of renal and of suprarenal origin possess no convincing structural similarity. (2) All the forms of the hypernephromata are varieties of one common type. (3) The renal hypernephromata originate in the epithelium of the kidneys.

Askanazy [4] objects to Stoerk's [30] statement that lumina are never found in the suprarenals of man. He gives a short résumé of the literature, and describes and figures two cases. One of these is a normal gland with numerous tubules in many parts of its cortex. Their lumina are regular, and contain traces of granular material and an occasional desquamated cell.* The other shows a large lumen in an adenoma. There are no signs of old hæmorrhage. The cells that line the lumina are identical with those of the suprarenals. The possibility of the presence of aberrant tubules of other origin is thus excluded. He concludes that lumina certainly do occur, although rarely, and that their presence in hypernephromata is not incompatible with Grawitz's theory.

Trotter,[34] in 1909, gives a full account of a typical renal hypernephroma. He says: "Personally I hasten to acknowledge that, though up to the time of reading Stoerk's paper fully acquiescing in the accepted views, I have been a good deal impressed by his arguments, and I think they may be added to." This he does by making the following points: (1) The hypernephromata are essentially tubulo-cystic in structure. The specimen shows clearly that the dominating perivascular arrangement is a secondary development, caused by degeneration of the cells at the centres of the alveoli with persistence of a peripheral zone of healthy cells next to the vessels. (2) The great relative frequency with which these tumours occur. To-day it would probably be almost justifiable to say that all primary epithelial tumours of the kidney, with the exception of those of the pelvis, are of this nature. This would leave us in the remarkable position of having to believe,

* Because of the presence of these cells, the possibility of some form of central degeneration of solid alveoli cannot, to my mind, be definitely excluded.

if we maintain Grawitz's hypothesis, that in a glandular organ so subject to malignant disease as the kidney, a true carcinoma of the gland substance does not occur.* (3) Many facts of the growth of these tumours are quite as consistent with the views of Stoerk as with those of Grawitz. For example, if the tumour originates in the convoluted tubules it must always be primary in the cortex; again, the convoluted tubules receive their blood-supply entirely through veins from the glomeruli, and the growth of the tumour will begin in the most intimate relation to the purely venous network surrounding these tubules. (4) What influence may we expect the original structure of an organ to exercise upon that of a carcinoma developing in it? It would seem probable *a priori* that the more elaborate the normal arrangement of the epithelium of a glandular organ is, the more complicated may we expect to be the picture which a carcinoma growing in it may present.

In the same year I [24] described a solid hypernephroma of the kidney, whose local recurrence after removal had a villous structure. I argued that a solid organ like the suprarenal could not produce villi.†

Steinke,[29] in 1910, opposes Stoerk [30] on the strength of a number of tumours of the suprarenals he examined in cattle. Accessory suprarenals and hypernephromata do not occur in the kidneys of these animals, whereas they are common in the suprarenals themselves. The converse obtains in man.‡ Eight of his tumours correspond in every particular, in their age incidence, their gross and histological structure, and their dissemination by the blood vessels, with the hypernephromata of the kidneys and suprarenals of man, even when these are of the tubular or cystic type.§ He concludes that these facts afford strong evidence of the origin of the human hypernephromata in suprarenal tissue, but is unable to explain why they

* Compare this statement and deduction with those made by Lubarsch [21] in the following year (see the introductory paragraph to this study).

† I have realised long since that these "villi" are spurious, and that they are caused by necrosis with survival of the cells within reach of the blood-supply, *i. e.* those next to the vessels of the branched septa of the tumour. These appearances can, of course, be produced in the most solid of organs. My position was very similar to that of the writers who maintain the specific entity of the "peritheliomata." I merely mention my juvenile effort here as a tribute to Stoerk. It resulted from the perusal of his paper. It is to him I owe my first doubts of the truth of Cohnheim's theory.

‡ Although some writers, notably Glynn,[13] were unable to find accessory suprarenals in the kidneys, others were more successful. Small "adenomatous" nodules occur with such regularity in man within or close to the suprarenals that they almost deserve to be regarded as normal structures (*vide* Study III.).

§ Steinke compares his tumours indiscriminately with those of the human kidneys and suprarenals. This is inadmissible in view of the marked differences of structure that obtain between the latter (*vide* especially Glynn [13]). Hypernephromata have not been found in human suprarenals except by Kostenko.[19]

are much more common in the suprarenals of cattle than in those of man, even when the fact is taken into consideration that displacements of cortex are much less frequent in human suprarenals.

Zehbe,[39] in the same year, corroborates Stoerk's [30] arguments. He concludes that the epithelial tumours of the kidneys, including the hypernephromata, orginate in compensatory hyperplasias of renal epithelium. Whereas the "foam" cells distended with globules of fat, the stroma consisting of little more than capillaries, and the giant-cells of the hypernephromata have their prototypes in the cells of the suprarenals as well as in those of the kidneys, other characteristic structures are found in the latter alone. These are the lumina and villi, the "glassy" cells that result from hydropic distension of the epithelium,* and small deeply staining non-degenerate cells often to be seen in hypernephromata and adenomata of granular kidneys, but never in the suprarenals. He emphasises more strongly than Stoerk [30] did the intimate connection between sclerosis of the kidneys and regenerative tumour formation; all the epithelial tumours of these organs he examined, including the hypernephromata, were associated with granular changes of the kidneys, whereas sarcomata and mixed tumours were often found in otherwise healthy organs. Two typical hypernephromata arose in the hilum of the kidney, where displacements of suprarenal tissue do not occur.†

Sisson,[28] in the same year, came to similar conclusions. In adenomata of the suprarenals the fat content of large numbers of cells is uniformly distributed as discrete granules of equal size. In hypernephromata it varies enormously in individual cells, both in its amount and in the size of the granules, which tend to become confluent. These differences are constant, and apparent in small tumours as well as in large ones. He examined several suprarenal tumours in cattle. They agree with the corresponding normal organs of these animals in not containing doubly refracting substance, one of the most constant constituents of human hypernephromata. Steinke's [29] argument, that they support Grawitz's hypothesis, thus falls to the ground. Sisson gives several reasons for his belief that the hypernephromata do not arise in hyperplasias in common with the adenomata of granular kidneys, but that they originate in congenital tissue malformations.

* Zehbe points out that connective tissue and endothelial cells, and probably leucocytes as well, undergo these changes, and explains the so-called hypernephromata of the skeleton on these lines.

† Aschoff [3] illustrates (Fig. 339, p. 472) a small hypernephroma inside a renal pyramid in his text-book.

Kostenko,[19] in 1911, defends the suprarenal origin of the hypernephromata. He compares them with adenomata and carcinomata of the suprarenals. They are identical with them in the following respects. (1) The structure of the epithelium; dark and vacuolated cells are always present. (2) The relations of the parenchyma to the stroma, especially the capillaries. (3) The presence of giant-cells. (4) True and false lumina and cysts are present in suprarenal as well as in renal tumours. Tubular and papillomatous structures, far from contradicting Grawitz's theory, support it. He describes an adeno-papillary cystoma, with spaces lined by columnar epithelium with goblet-cells and secretion of mucin, in an otherwise healthy suprarenal of a man of 22. Transitions can be seen betwen its cells and those of the cortex.* The buds of epithelium that project into the vessels of the suprarenal and of its tumours are always covered by endothelium. They are, however, easily torn away.†

A paper by Wilson and Willis [37] appeared in 1911. They agree with Stoerk [30] that no kind of convincing agreement exists between tumours of the suprarenals and hypernephromata of the kidneys, and that all the forms of the latter are varieties of a common type, but are not prepared to accept his third conclusion, that they are derived from the epithelium of the kidneys. Two theses are upheld in this paper. (1) The accessory suprarenals in the kidneys are of the nature of Wolffian tubules. "With regard to the frequency with which true adrenal rests occur within the kidney I have long entertained considerable doubt. When one examines microscopically the small, whitish, ovoidal masses which are encountered underneath or within the kidney capsule, he is struck with the resemblance of most of them to the remains of the Wolffian body. Indeed, there is reason to doubt whether any of the so-called adrenal rests within or beneath the kidney capsule are really of adrenal origin,‡ when one considers the embryological development of

* *Vide* footnote to Sudeck's [31] paper.

† *Vide* Manasse,[22, 23]. Some of Kostenko's statements are sorely in need of corroboration. Whereas carcinomata of the suprarenals are distinguished by a marked want of similarity to the cortex of the gland, a fact pointed out by Stoerk,[30] Glynn,[13] etc., and one with which I fully agree, some of his figures might almost be taken to represent normal suprarenal. Again, the identity of his Fig. 13, drawn from a carcinoma of the suprarenal, with a hypernephroma of the kidney is at variance with the statements of a number of writers. He ignores completely all the possible points of resemblance of the hypernephromata to the kidneys and to renal tumours. The criticism is a fair one to make that his paper is entirely biassed and one-sided.

‡ I do not know what the structures are that Wilson and Willis refer to, since they do not tell us the reasons that have caused them to doubt. I can but conclude that they are totally different from the accessory suprarenals in Figs. 23–26 (III.). Their theory bears a certain resemblance to that of Aichel [2] on the development of the suprarenals, a theory that has found no support.

the two organs" (p. 80). They next produce embryological evidence that, during the earlier stages of their development the kidney and suprarenal are separated by the entire thickness of the degenerating Wolffian body. They come into final apposition only by the gradual atrophy of the latter. Long before this they have each acquired a capsule. Indeed, it is difficult to conceive how any part of the adrenal cortex can, during the process of development, become imbedded within the parenchyma of the kidney without being separated from it by three distinct laminæ of fibrous tissue, the first derived from its own capsule, the second from the remains of the Wolffian body, and the third from the renal capsule.* The very frequent inclusion of remains of the Wolffian body within or under the renal capsule would lead one to expect the much more frequent development of tumours from this source than from the suprarenal. But unfortunately for this hypothesis the histology of the Grawitzian tumours rarely shows tubules of the broad open type of the Wolffian body, except where they have been distended by secretion. (2) Remains of nephrogenic tissue are observed in the kidneys of embryos and even in the first years of life. Their fate is by no means determined.† The hypernephromata are the result of proliferation of islets of the renal blastema, which have persisted in the cortex of the adult kidneys and are excited to begin anew their embryonic development.‡

Glynn's [13] paper, which was published in the following year, is second in importance to none, not even to that of Stoerk.[30] He draws attention to certain biological properties of the epithelial neoplasms of the suprarenal cortex, the result of the physiological activity of their cells. They have been known since they were pointed out by Bulloch and Sequeira,[8] but their bearing upon the histiogenesis of the hypernephromata has not been appreciated. They produce a diminution of female and the development of certain male characters in women before the menopause, as well as precocity in children of either sex. These changes are also met with in simple hyperplasias of the suprarenal cortex. Since they are never associated with hypernephromata of the kidneys, the origin of the latter from

* I suggest that these layers may reasonably be expected to fuse at a later stage of development, and that the capsule that often surrounds accessory suprarenals may be formed in this way. Its frequent absence may be the result of atrophy.

† *Vide* Study V. p. 59, footnote.

‡ Wilson and Willis thus determine their fate for them to their own satisfaction (*vide* Study V.). For thesis 2 we must rely entirely on their word. Their paper is a typical instance of theories based solely upon inductive reasoning unsupported by evidence, and of the lengths to which Cohnheim's followers are prepared to go.

accessory suprarenals is disproved.* Glynn is the first to point out fully and adequately the marked histological differences between carcinomata of the suprarenal cortex and renal hypernephromata, and supports his arguments by excellent photographs.†

Ipsen,[17] in 1912, critically examines all the characters of the hypernephromata and carefully weighs the evidence for and against Grawitz's theory provided by them. His verdict is uniformly against it. He believes that the cysts are caused by hæmorrhage. Many of the papillæ, which are often branched, are true, *i. e.* their ends are free. Unlike most writers, he urges that those parts that possess a villous structure are the youngest, least altered parts of the tumour. They are identical with certain types of the villous adenomata of the renal cortex, except in the vacuolation of their epithelium. But this is sometimes absent. The vacuoles are occupied almost entirely by fat. Hydropic degeneration is not as prevalent as Stoerk [30] believed, since many of the empty spaces seen in frozen sections stained with Sudan are caused by the fact that the larger drops of fat are torn out of them in cutting the tissue. Ipsen points out that the amount of fat seen in histological sections is no index of the total quantity present. Hypernephromata, whose cells showed much fat when stained with Sudan, were found upon chemical analysis to contain about 10 %, whereas a pulmonary metastasis of a carcinoma of the colon with considerably less fat that could be detected with the microscope contained 15 %, and a normal horse's suprarenal, used as a control, contained 31 %. Nor do the phosphorus and cholesterin contents of the fats allow of deductions, since they are very

* The only possible objection to this is the one that failure of the changes to appear depends upon the degree of anaplasia or loss of physiological function of the cells of hypernephromata. But the differences that exist between carcinomata of the suprarenals and hypernephromata of the kidneys, many of which, by the way, are innocent, are much too radical to be accounted for in this way.

† Glynn's merit lies in the fact that he has corroborated the histological evidence by means of physiological data. Prof. Glynn applies the name of hypernephroma to the suprarenal as well as the renal neoplasms. In a later paper [14] he calls the former hypernephromata and the latter "hypernephromata." But, in spite of Adami's [1] (p. 747) arguments, malignant tumours of the suprarenals are genuine carcinomata, quite as much as those of the kidneys or of Mueller's duct, or indeed of any epi- or hypoblastic organ (I hope to substantiate this statement in my paper on the relationship of development to tumour formation). I therefore prefer to speak of them as carcinomata, and to retain the term hypernephroma for the renal tumours. This I do without prejudice to their histiogenesis, but simply to commemorate the interesting history of the subject. The habit of French writers who refer to a carcinoma of the liver as a hepatoma, and to one of the testicle as a seminoma, etc., has little in its favour.

I have not referred in this paper to the deductions drawn from the absence of adrenalin in hypernephromata, since it appears to be confined to the medulla of the suprarenals.

similar in hypernephromata and in other tumours, as well as in the kidneys and the suprarenals. Those areas of the hypernephromata which, on the whole, most closely resemble the suprarenals are least suited for the study of their histiogenesis, since they are probably always the most altered and degenerate parts.*

Dunn,[10] in 1913, found accessory suprarenals, adeno-papillary structures and papilliferous cysts in the kidneys of several cases. The last of these were often multiple, and the organs were the seat of chronic interstitial changes. He concludes that any of these structures might conceivably give rise to malignant tumour formation, but of the three the papillary cysts, from their peculiar histological features, suggest themselves as the most probable origin of the tumours of the Grawitz type.†

Wilson,[36] in 1913, wrote a second paper, in which he amplified his conclusions of 1911 [37] in the following sentences: " Failure of the nephrogenic vesicles to form a tubular connection with the collecting tubules is responsible for the condition of congenital cystic kidney. A study of the development of the nephrogenic vesicle, however, has convinced me that such a failure in its embryonic development is responsible for much more than the formation of renal cysts. Primarily, the nephrogenic cap consists of somewhat darkly staining, round, and irregularly arranged embryonic cells. In the first stage of the formation of the vesicle it is a solid mass of cells which is frequently somewhat elongated and presenting a cordon-like appearance. In its second stage it is first an ovoidal vesicle and then a tubule. Now all these embryonic pictures closely resemble those which we find making up the histologic elements of the Grawitzian tumours " (p. 527). " As far as its embryologic relationships are concerned, the renal capsule is frequently the site of inclusions from the mesonephros—and occasionally, though rarely, of inclusions from the suprarenals. In the early stages of capsular development, the degenerating tubules of the Wolffian body lie in immediate apposition to, or commingled with, the embryonic connective-tissue fibres which enter the formation of the capsule. Consequently the inclusion of masses of degenerating Wolffian tubules in the renal cortex is very easily understood. We have in our series one well-marked case

* This paper contains the most clearly and impartially written analysis of the hypernephromata that I have read, and is well worthy of study. It produces the impression that Ipsen retained an open mind throughout his investigations.

† This is the first paper based upon the study of small renal tumours published in this country in confirmation of Sudeck's [31] arguments, after an interval of twenty years.

of this type, that is, an encapsulated mass of Wolffian tissue lying within the renal cortex" (p. 528).*

Beckmann,[5] in 1915, describes a suprarenal with many very irregular branched and anastomosing lumina, bounded and often sub-divided by angular cells. They look as if they had been produced by some "burrowing" agency. They result from the accumulation of fluid within originally solid masses of epithelium. He assumes the fluid to be the internal secretion of the gland, which normally passes directly into the blood or lymph. He compares it with the internal secretion of the thyroid, and points out the importance of his observation for the question of the histiogenesis of the hypernephromata.†

Gerlach and Gerlach,[12] in 1915, agree with Stoerk[30] and others that all hypernephromata are merely varieties of a single type. But they go a step farther than this, and show that it is impossible to separate them satisfactorily from other (malignant) tumours of the kidneys. They can find but one structural character that appears to prove Grawitz's theory. This is the presence of solid groups of cells in the alveolar forms, separated from each other by anastomosing septa which consist of capillaries usually surrounded by a minimal amount of connective tissue. A very close resemblance indeed to the suprarenal cortex is thus produced. Among others, there are two points that are particularly incompatible with this theory. These are: (1) The presence of true lumina, with a true secretion inside them. They are never found in the suprarenals or in the tumours of these glands, although pseudo-lumina, caused by necrosis of epithelium or by liquefaction of the stroma are met with. (2) The large, clear, "glassy" cells resembling vegetable tissue. They are always absent in tumours of the suprarenals. They are not artefacts, as suggested by Ipsen,[17] but are caused by the presence of glycogen and cholesterin-esters. It thus appears that the solid alveolar hypernephromata consist of suprarenal cortex, whereas the tubular and villous forms

* It is a thousand pities that Wilson has omitted to describe or figure this unique specimen. It is the only piece of known evidence that Wolffian tubules are ever found in the kidneys. It must be admitted that, in his paper of 1911, he demonstrated the theoretical possibility of their inclusion by the aid of embryological material. But he failed to demonstrate their actual presence in the renal capsule. With regard to Wilson's first argument: I can only say that I have never seen a hypernephroma, nor have I ever read a description or examined a picture of one that bears the slightest structural resemblance to the renal blastema.

† This paper was written in Askanazy's laboratory. I have not been convinced by these arguments. Are inter-cellular spaces formed by the burrowing action of a fluid, as Beckmann very aptly describes them, true lumina? He has failed to show that the fluid is not lymph. His comparison with the thyroid is not a happy one. Here the colloid is a normal constituent of the gland. Nor is it apparently the active internal secretion, but the vehicle or medium to which it is bound.

resemble papillary carcinomata and adenomata of the kidneys, and therefore originate in renal tissue. But intermediate stages frequently occur. They indicate that many hypernephromata are mixed tumours, whose protophase is a double one, derived partly from suprarenal, and in part from renal cells. This view was suggested by Ricker,[27] who believed that renal tubules included in the suprarenal could undergo blastomatous proliferation, and has since been advocated by more than one writer. But Gerlach and Gerlach only accept it in so far as it indicates the presence of an error of development. Such developmental errors are common in the kidneys. They are represented, on the one hand, by accessory suprarenals (choristomata), and on the other by the small cortical cysts of infants (hamartomata). The latter often give rise to papillomata. Both kinds of anomaly lead up to the hypernephromata. The developmental disturbance that has caused them can therefore only have taken place at a time when cells were present that possessed the prospective potentialities of suprarenal and of renal tissue. These are the cells of the mesoderm, from which both organs are developed. The suprarenals undergo their development in close contact with the meso- and metanephros, and we need only assume an abnormal union of one or more mesodermal cells destined to form suprarenal cortex with others that are to give rise to the kidney. They are inclosed together within this organ in an undifferentiated, dormant state, in which state they remain until stimulated to blastomatous proliferation by some unknown agent. If differences in the time at which the malformation has occurred and of the composition of the resulting embryonic " rest " be allowed for, all the aberrant structures of the renal cortex,—from accessory suprarenals, through the hypernephromata, the papillary carcinomata and the small adenomata, to the simple cysts of infants,—are readily explained. Together with Grawitz they regard the hypernephromata as typical examples of tumour formation arising in developmental aberrations.*

Wright,[38] in 1922, takes a diametrically opposite view. He gives a very careful description of the histological structure of renal hypernephromata. He insists that the formation of papillæ is a constant and essential feature of most new growths

* We thus have not only a Grawitz theory, but a hyper-Grawitz theory as well, a typical explanation upon the lines of Cohnheim's hypothesis. It is well argued and impossible to disprove. But I have tried to show in the preceding studies that it is equally impossible to prove it, and that the evidence that warrants the central assumption upon which it is based, amounts practically to nothing. It errs in its disregard of the almost constant association of all these tumours with chronic nephritic changes.

arising in the renal cortex, and that it is one of the ways in which the kidneys react to the "neoplastic stimulus." The form of reaction called "hypernephroma" may accompany all the others; that is to say, it has been found in tumours of the papillary adenomatous and the papillary carcinomatous type. Owing no doubt to differences in the exact nature of the irritant which is a necessary preliminary to tumour formation, the type of new growth will, in one case, be a papilliferous cyst which may progress to the usual hypernephroma form, in another there will be a papillary adenoma also producing hypernephroma-like cells. The end-result, which is called hypernephroma, is a papillary one. Wright declares emphatically that these tumours cannot originate in a "rest" of any kind, either suprarenal, or renal; they can only arise in the epithelium of the kidneys.

PART II

I have tried to show in Study V. that developmental anomalies are generally not predisposed to tumour formation. Neoplasms, whose structure is such as to necessitate the assumption that they have originated in a "cell-rest," are infinitely less common than others, in the case of which this assumption is purely hypothetical. I concluded that the cells of congenital malformations are merely not immune to tumour formation.

How does this reasoning apply to the hypernephromata? Here again we are faced with the question: Are we entitled to assume that they arise in cell-rests or not? We have seen, from general considerations, how difficult if not impossible it would be to show with any degree of certainty that they do, or do not, arise in renal cell-rests. If, therefore, it could be proved that they originate in accessory suprarenals, brilliant confirmation of Cohnheim's theory would have been provided, especially since they are essentially tumours of middle age. We can therefore neglect hypotheses like that of Gerlach and Gerlach,[12] which give us no help in answering the question, and limit ourselves to Grawitz's original proposition.

The subject ought to be approached with an unbiassed mind. This I confess that I am quite unable to do. For me the controversy was settled by Stoerk,[30] and finally buried by Glynn,[13] and the suprarenal origin of the hypernephromata disproved. This is the reason why I have abstracted the papers on the subject *in extenso*, and allowed each writer, as it were, to speak for himself.

Grawitz's hypothesis is founded upon three considerations:

(1) Accessory suprarenals are found in the kidneys, and hypernephromata are found here as well. (2) The arrangement of the cells of the hypernephromata corresponds with that of the suprarenal cortex. (3) The structure of their individual cells is identical with that of the epithelium of the suprarenal cortex.

Grawitz's first proposition is based upon common knowledge and cannot be contradicted. Accessory suprarenals are, however, by no means as common in the kidneys as he supposed. A careful observer like Glynn [13] was unable to find them. My own experience has been referred to in Study III. The estimate that they are present in from 1 to 2 % of post mortems approximates to the truth. Hypernephromata are not common either. Their frequency is about proportional to that of accessory suprarenals, and certainly does not vitiate Grawitz's reasoning. But Stoerk,[30] among others, has shown that the distribution of accessory suprarenals does not correspond with that of the hypernephromata that are small enough for us to be able to deduce in which part of the kidney they have arisen. If accessory suprarenals and hypernephromata were cause and effect, their distribution should be identical. The former have never yet been found within the pyramids, whereas several hypernephromata have been described here (Aschoff,[3] Zehbe [39]). Grawitz has therefore failed to establish a certain connection between these displaced tissues and the tumours that he believed to arise in them.

Grawitz's second proposition must also be granted. The cells of the hypernephromata are usually arranged in alveoli or groups that are separated from each other by capillaries surrounded by an imperceptible amount of connective tissue. This architectural plan is identical with that of the suprarenal cortex. But it by no means follows that hypernephromata must therefore actually be tumours of displaced suprarenal cortex, as a glance at Fig. 56 will show. Here I have drawn side by side a piece of the renal cortex, of that of the suprarenal, and of the liver under the same magnification. The former consists of urinary tubules imperfectly separated from each other by capillaries, the suprarenal of solid groups of cells similarly limited, and the liver of branched columns of cells, projecting into blood-spaces, whose endothelial lining is incomplete. The relations of the epithelium to the vessels are fundamentally identical in the three organs. They cannot, therefore, be used in proof of the suprarenal origin of the hypernephromata.*

Grawitz's third proposition is a dangerous one to uphold, since it is a difficult matter to prove identity of structure, and

* See also above, the 3rd argument of Trotter.[34]

even should this have been proved, to argue that there must necessarily be identity of histiogenesis. But the so-called structural identity of the cells of the hypernephromata and of those of the suprarenals depends upon nothing more convincing than the presence of vacuoles filled with fats and lipoids, hydropic fluid, glycogen, and possibly other substances as well. These are all of the nature of paraplasm that is stored in the cells, if indeed some of them are not simply degeneration products. That differences are found between these substances in hypernephromata and in the suprarenals is probable. Their presence cannot be taken as a sign of a specific physiological activity of

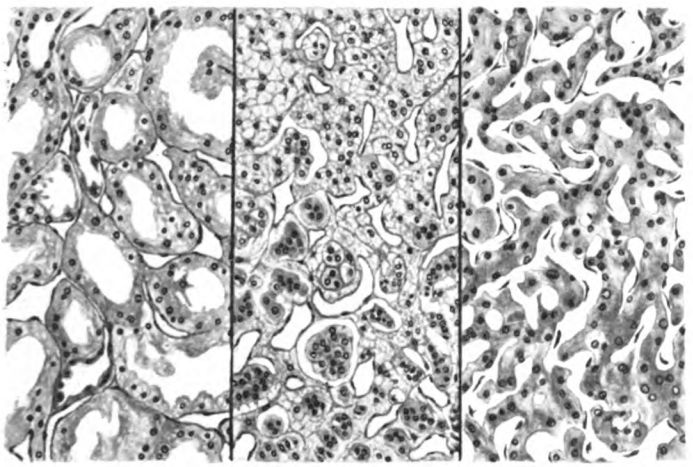

FIG. 56.
Kidney, suprarenal cortex, liver. Magnif. 180.

the cells. Bulloch and Sequeira [8] have shown that an important function of the cells of the suprarenal cortex is the influence they exert upon metabolism, and upon the growth of the body and the development and maintenance of certain secondary sexual characters. When the suprarenal cortex is increased in bulk these substances are produced in excess, and characteristic disturbances, named " suprarenal virilism " by Glynn,[14] are the result. These changes are present in carcinomata of the suprarenal cortex, but are invariably absent in hypernephromata of the kidneys, as was pointed out by Glynn.[13] * Since these tumours never produce the only biological effect that we are able to associate with the suprarenal cortex, the last argument

* I have records of five hypernephromata of the kidneys of women between the ages of 23 and 48. Not one of them showed signs of suprarenal virilism.

in favour of their identity fails. There is no evidence whatever in support of Grawitz's third proposition.

We can therefore reasonably and safely conclude that Grawitz's theory of the origin of the hypernephromata in accessory suprarenals has not been proved. This attractive hypothesis, which at one time was accepted without question by all pathologists, and whose popularity it has taken nearly forty years to lessen, appears to have been built upon foundations no firmer than coincidence; the accidental resemblance of the cells of hypernephromata to those of accessory suprarenals, and the presence of both in the kidneys.

My task is thus virtually ended. No other epithelium remains in which these tumours can arise, except that of the kidneys. For there is absolutely no evidence whatever that mesonephric tubules are found in these organs, as suggested by Wilson and Willis.[37] They showed by means of embryological material that there are theoretical reasons to expect them here, but failed to demonstrate their actual presence. Bare statements like the one that one is struck with the resemblance of most of the sub-capsular nodules to Wolffian remnants, or that an encapsulated mass of Wolffian tissue lying within the renal cortex was found in one of a series of cases,[36] are not evidence upon which I can form an opinion of my own. It is therefore waste of time for me to consider them. I again find myself in agreement with Lubarsch,[20] who refuses to entertain a theory based upon a purely hypothetical "cell-rest." This, as I have already said, applies with equal force to that of Gerlach and Gerlach,[12] and to similar hypotheses concerning the dual origin of the hypernephromata.*

I may, however, be allowed to give a few illustrations of the relationship of the hypernephromata to adenomata of the kidneys, and to indicate the intimate association of the latter with chronic nephritis, although the second of these subjects is, strictly speaking, outside the scope of this paper.

If hypernephromata are renal adenomata, whose cells have undergone fatty and hydropic changes or, as Wright [38] happily expresses it, have undergone the "hypernephroma reaction," they ought to contain areas in which these changes have not taken place; areas whose cells have retained their original structure. It is often very difficult to find these areas, since it is the general rule that the changes are so extensive that the cells that have escaped them are easily overlooked. Yet they can generally be found, and have been described by most observers. Their cells

* I have not thought it worth my while to discuss these in the first part of this paper.

are the small dark cells of Zehbe [39] which, as this writer points out, are not found in the suprarenals. They are unusually

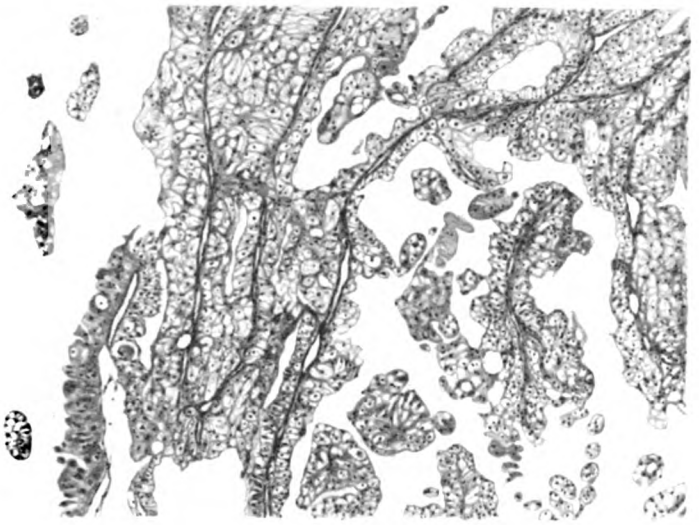

FIG. 57.
Metastasis in cervical lymph-gland of hypernephroma of kidney. Magnif. 90.

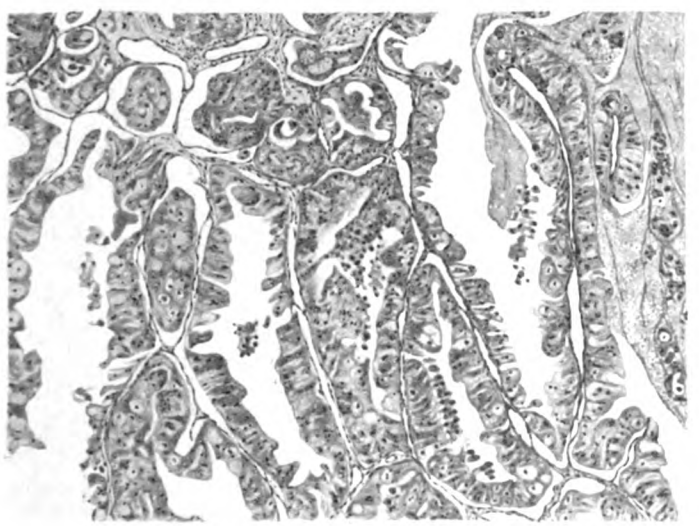

FIG. 58.
Contiguous field of same, with structure of alveolar carcinoma. Magnif. 90.

apparent in the specimen illustrated in the accompanying drawings.

Figs. 57 and 58 represent contiguous areas of a secondary

deposit of a hypernephroma of the kidney in a cervical lymph-gland. (The space on the left-hand side of Fig. 57 represents the other side of the right-hand one in Fig. 58.) The first drawing shows a typical hypernephroma with solid alveoli, tubules, and cystic spaces with villous projections. Nearly all the cells are vacuolated. Fig. 58 shows a carcinoma composed of originally solid alveoli of deeply stained cubical and columnar cells, which have acquired lumina and been converted into large spaces by hæmorrhage and necrosis of the central cells. The alveoli are separated by narrow branched connective tissue septa with thin-walled capillaries. The epithelial cells are uniformly protoplasmic, only every here and there is one of them swollen, glassy, and vacuolated. This appearance is retained by them in the lower part of the left-hand side of Fig. 57, where the abrupt change into typical hypernephroma tissue can readily be made out. I submit that Fig. 58 represents a younger, less altered part of the tumour than Fig. 57, since the alveoli are smaller, and their conversion into spaces by reason of central necrosis is indicated; the cells have here retained their original uniform protoplasmic appearance. Ipsen's [17] statement that the areas of the hypernephromata which resemble the suprarenals most closely are the least suited for studies in histiogenesis is amply borne out by this tumour.

Fig. 59 represents part of the periphery of a sub-capsular tubular adenoma of a granular kidney, about 1 cm. in diameter.* It is quite typical and requires no detailed description. The stroma which, as was pointed out by Ricker,[27] is always much more abundant at the periphery than nearer the centre of these tumours, is well marked. Fig. 60 has been taken from the centre of this adenoma. At first sight it appears to consist of alternating areas of two tissues. One of these has retained the structure of a tubular adenoma; its cells are deeply stained and protoplasmic. The other is a typical solid hypernephroma, whose swollen cells, in suitably stained sections, are found to be loaded with fats and lipoids. Many of these areas are bounded by narrow strands of connective tissue and by capillaries, and are quite distinct from each other. In the upper part of the drawing there is, however, evidence that the cells of the hypernephroma are altered swollen adenoma cells. All the cells of a tubule or of a group of tubules have, in most cases, undergone the " hypernephroma reaction " together. No specimen could corroborate the renal origin of the hypernephromata better than this.

* For this priceless specimen I am indebted to Dr. J. R. Perdrau, of the Lambeth Infirmary.

I cannot satisfy myself that the tubules and cysts of the hypernephromata are truly primary, and that they are not the result of hæmorrhage, accumulation of fluid, be this of the nature of lymph or of a true secretion analogous to urine, and of necrosis of central cells. Although these tumours are essentially adenomata, the spaces seem to me to be always secondary. We have seen that the typical appearance of the

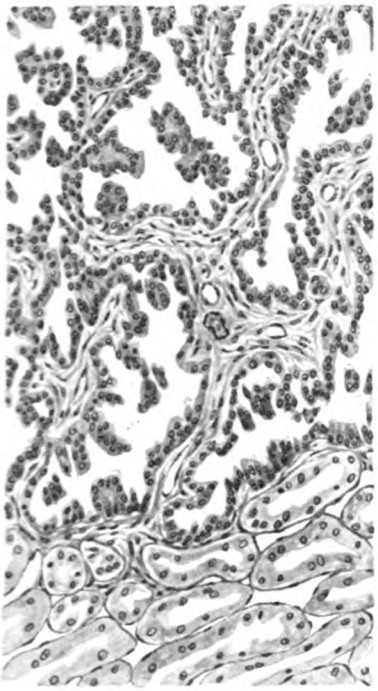

FIG. 59.

Edge of adenoma of granular kidney. Magnif. 180.

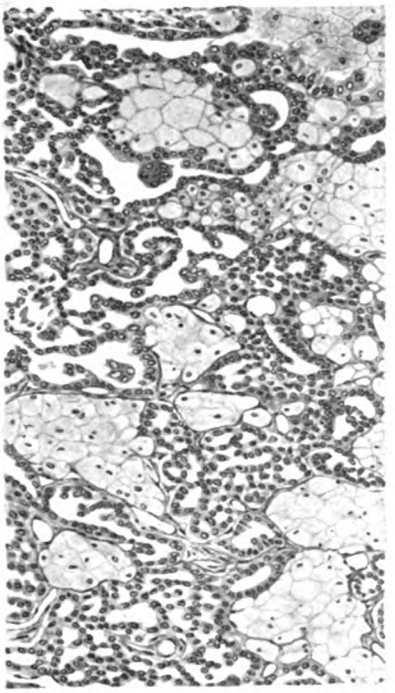

FIG. 60.

Centre of same. Alternating areas of tubular adenoma and hypernephroma, and transitions between them. Magnif. 180.

cells of hypernephromata is caused by an increase of their bulk that results from the accumulation of certain substances inside them. In the specimens that I have examined the swelling is always so great, and affects whole alveoli in so uniform a manner, that the lumina of the pre-existing adenoma are invariably obliterated. Fig. 60 illustrates this remarkably clearly.

Once a space has been formed, the conditions become such that folding of the peripheral cells which now line it can take place into its interior. This causes folding of the stroma which, as we have seen, consists of little besides capillaries. I do not

see how the endothelial cells of the latter can fail to proliferate at the point where they are folded and thereby irritated. This will assuredly result in the formation of endothelial buds which, becoming channelled, will give rise to new capillaries. These will enter the folds and follow their irregularities and branches, and produce the villi characteristic of the hypernephromata. But a young capillary that is budded off from a pre-existing one always strives, if I may use this expression, to form anastomoses with its neighbours. The vascular loops of granulation tissue are produced in this way. This is the *raison d'être* of capillaries, a character inherent in those of hypernephromata to an equal degree with those of all other tissues. All the conditions for the formation of true papillæ are thus present even in neoplasms arising in the most solid organs, provided that pseudo-lumina are first formed in some way or other. Their presence in hypernephromata appears to me to form no contradiction to Grawitz's theory.

It appears from these considerations that the presence or absence of lumina in the suprarenal cortex is, in my opinion, quite immaterial to the question of the histiogenesis of the hypernephromata. I have no wish to discredit Kostenko's [19] account of lumina and papillæ in carcinomata of the suprarenals, although I should like to see some of his statements confirmed.

I have for years collected all the small nodules of the kidneys that have come my way at post mortems. Among them there is a goodly number of adenomata of the cortex. These were, without exception, found in diseased organs. The kidneys were usually quite obviously granular; in a few cases the adenoma was in a scar which, on histological examination, was packed with fibrous glomeruli, the remains of an old infarct. I can therefore corroborate Stoerk [30] and the writers who emphasise the intimate association of cortical adenomata with chronic interstitial nephritis. Since these little nodules are peculiarly well adapted for the study of the connection that exists between regenerative hyperplasia and tumour formation, I intend to use them extensively in the chapter on this subject. For the present I can but reiterate with Stoerk [30] that they are advanced stages of regenerative hyperplasia which have reached, and in many cases passed, the rather indefinite borderland that separates this condition from fully established tumours. Why otherwise should they be common in diseased kidneys, whereas not more than a few have been described in healthy organs, especially in children? I would here point out the mistake that writers make who neglect a constant association of this kind. Even though Braunwarth [7] found three adenomata and five cysts

with various degress of proliferation of their epithelium and papilla formation in the kidneys of infants, it does not follow that every one of these tumours in granular kidneys of adults has originated in a congenital cyst or malformation.

There remains for me to say a few words upon the so-called "extra-renal hypernephromata." They have been described mainly in three regions of the body: The bones, the ovaries and broad ligaments, and the liver. Accessory suprarenals have been found frequently near the ovaries, rarely in the liver, and never in the bones.

Because of the absence of displacements of suprarenal cortex in the skeleton I need not waste time over the hypernephromata of bones, more especially since they have been referred to in the first part of this paper (*vide* Driessen,[9] Pick,[26] Zehbe,[39] and the footnotes to their papers). All the recorded cases that are not secondary to a hypernephroma of the kidney are connective tissue tumours, whose cells have undergone infiltration with fats and with glycogen, and have thereby acquired an accidental resemblance to those of the suprarenals.

Luckily for me, Prof. Glynn [14] has recently written an exhaustive paper on the so-called hypernephromata of the female pelvis. He shows that a considerable number has been described in the ovaries, where suprarenal rests have never yet been demonstrated with certainty. On the other hand, only a few instances have been recorded in the broad ligaments, where accessory suprarenals are common, at all events in infants. He concludes, after careful study of their morphological structure and their biological properties, that the evidence points to the deduction that all the recorded cases (with the exception of one, presently to be referred to) are actually composed of luteal tissue, whose histological resemblance to renal hypernephromata, although close indeed, is purely secondary and accidental.

Within the liver accessory suprarenals have only been found on the lower surface of the right lobe, in and close to the suprarenal impression (*vide* Studies III. and IV.). If true suprarenal neoplasms occur in this organ, they must originate in this lobe.

Fig. 61 represents a section of a large, soft, pale yellow, hæmorrhagic, nodular tumour, whose blunt ramifications and shallow elevations had replaced the whole of the right lobe of the liver of a woman of 68. At first sight the drawing could easily be mistaken for one of a solid hypernephroma of the kidney. But rows and columns of deeply stained epithelium are present every here and there; they consist of unmistakable liver cells. They are most numerous in the upper part of the

figure. There can be not the slightest doubt that they are cells of the tumour. In spite of its naked-eye appearance and histological features this case is therefore a primary carcinoma of the liver.

Some time ago I collected the literature of these "hypernephromata" of the liver, with the object of writing a paper on them. It is unnecessary for me to discuss every case here, since not one is above criticism. I will but mention a couple. Pepere's [25] is the best known of them all. It arose primarily in

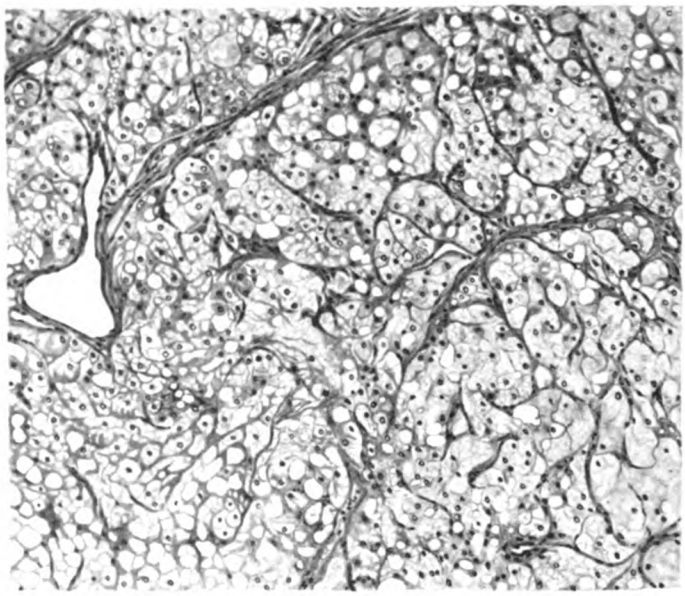

FIG. 61.

Primary carcinoma of liver resembling hypernephroma. Magnif. 95.

the left lobe of the liver, and had given rise to multiple secondary deposits in its right lobe. Because of the marked resemblance of its vacuolated epithelial cells that form double columns inclosing central lumina, surrounded directly by capillaries, to the medulla of the suprarenals, he concludes that it must have originated in an accessory suprarenal. In addition to the fact that displacements of these organs are only found in the right lobe of the liver, none of Pepere's arguments are convincing. Liver cells are very liable to become fatty and vacuolated. Bile containing central spaces or lumina are found among the cells of the liver and of its carcinomata. The disposition of the capillaries is no proof of a suprarenal origin (*vide* Fig. 56). After reading this paper I concluded that there was not sufficient

evidence for Pepere's view. Shortly afterwards I had the satisfaction of being told by Dr. Peyron, in whose possession the case then was, that it is an undoubted primary carcinoma of the liver. White and Mair's [35] case occupied the left lobe of the liver, and had spread into the right lobe by way of the portal vessels. Its cells contain fat and glycogen. They are arranged in columns and alveoli, with or without lumina. These often contain a homogeneous material resembling colloid, which is deeply bile-stained in places. The columns and alveoli are separated by capillaries, upon whose walls their cells rest directly. This case suffers from an additional objection to those urged against Pepere,[25] since it is probable that the colloid material, that was often stained with bile, actually consisted of this secretion.

This finishes what I have to say about the hypernephromata. Although Grawitz's theory may not have been disproved to the satisfaction of everyone, I submit that it has most certainly not been established, and that a tumour of the kidney has yet to be described, whose structure and behaviour are the same as those of the epithelial neoplasms of the suprarenal cortex. Renal hypernephromata do not indicate that accessory suprarenals, which are found with a greater or lesser degree of frequency over a comparatively wide area of the body, are pre-disposed to tumour formation. The only case that satisfies the requirements of a genuine epithelial tumour of an accessory suprarenal is that of Bovin.[6] It was found, not in the kidney, but in the broad ligament of a woman of 28, who for nine years had suffered from symptoms of suprarenal virilism, which improved after removal of the tumour. Should such a neoplasm ever be described in a kidney, let us hope that it will be in a child, or in a woman before the onset of the menopause.

Conclusions

The hypernephromata of the kidneys arise in the renal epithelium. No instance has been described whose origin in suprarenal tissue, assumed by Grawitz, is assured.

This is true generally of the so-called extra-renal hypernephromata. Although these tumours, with the exception of those of the skeleton, have been described in parts of the body in which accessory suprarenals occur, a connection with these malformations has been established in one case only.

Accessory suprarenals are therefore not predisposed to blastomatous growth, and the hypernephromata give no support to Cohnheim's theory.

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UROTROPINE AS A BILIARY ANTISEPTIC

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THE exact results of administration of urotropine by the mouth have come so frequently under discussion since Nicholaier [1] first introduced the drug into therapeutics in 1894, that one may be forgiven, in reopening the subject, for reviewing very briefly the position as it now stands.

Urotropine is a relatively stable substance resulting from direct combination of formaldehyde with ammonia. When taken by the mouth the drug is rapidly absorbed and excreted unchanged, chiefly in the urine, but, as mentioned later, it has also been definitely found in the bile. Some observers have detected its elimination in the cerebro-spinal fluid, saliva and bronchial secretions, whereas others have failed. In these doubtful situations it is possibly only a question of dosage.

As an internal antiseptic the action of urotropine, whatever its site, is considered always to be the same. In solution it tends to exist in a state of partial dissociation into its original components, the degree of dissociation depending upon the hydrogen-ion concentration of the solution and upon its temperature.

As far as urine is concerned, observations such as those of Martindale,[2] Jordan [3] and others have proved conclusively that for a completely germicidal quantity of free formaldehyde to be at once generated in urotropinised urine, the acidity must be relatively high, *i. e.* the hydrogen-ion concentration must be about $PH_{2\cdot5}$, and that to produce such acidity considerable doses of acid sodium phosphate must be given to the patient at the same time. No free formaldehyde and no antiseptic effect can be detected if the urine is alkaline or neutral. More recently Bloedorn and Houghton [4] have shown that raising the acidity of a urotropine solution increasingly favours the liberation of formaldehyde. In a neutral solution, or, in terms of hydrogen-ion concentration, at PH_7 no dissociation can be recognised. Except urine, all other secretions are almost invariably faintly alkaline or neutral in reaction. Therefore they conclude that if urotropine depends for its antiseptic action

upon the liberation of formaldehyde, this action can never be manifested except in the genito-urinary tract. Such has, indeed, for some time been a commonly accepted view.

On the other hand, there is some clinical evidence that urotropine given by the mouth is useful in the treatment of cholecystitis. Chauffard [5] strongly recommended it in his book on Gallstones, first published in 1913, and Hurst [6] described the good effects it had in cholecystitis in a clinical lecture published in 1914. The drug is now widely used both in England and abroad for diseases of the gall-bladder in spite of the fact that the possibility of its acting as a biliary antiseptic has been repeatedly denied on theoretical grounds.

In view of this somewhat conflicting evidence, an attempt has been made to investigate the action of urotropine when present in infected non-acid body fluids.

My chief consideration has been its effect in the bile, because there appears to be no doubt that urotropine given in therapeutic doses by the mouth does in part leave the body by this route. In 1908 Crowe [7] first proved the fact in the case of a number of patients with biliary fistulæ and in dogs and rabbits. He also noted that the bile of those infected with *B. coli* and *B. typhosus* tended to become sterile after administration of urotropine. At the outset of these experiments I administered by the mouth to normal guinea-pigs a dose of gr. 3 urotropine, and found when the animals were killed one hour later that it was possible in each case to recover small quantities of formaldehyde by distilling the gall-bladder bile with dilute mineral acid. In 1911 Chauffard [8] confirmed this mode of excretion in human beings by testing the bile of five patients upon whom cholecystostomy had just been performed. I have recently obtained positive tests for formaldehyde in the distillate from the bile in each of three cases under the care of Dr. A. F. Hurst in Guy's Hospital and New Lodge Clinic, and from whom, after the administration of nightly doses of urotropine varying from 20 to 90 grains, Dr. Hurst was kind enough to send me samples of bile collected in the morning by means of the duodenal tube.

Summary of Experiments

(1) *Effect of Acidity on Urotropine*

To decide under what conditions a solution of urotropine might be expected to commence dissociation at body temperature, the direct effect of increasing acidity was first tested.

Each of a series of solutions in water of increasing PH value

(Sod. Acid Phosphate) was made to contain 0·1 per cent. urotropine. These tubes were allowed to remain in the 37° C. incubator for some hours and at intervals tested for free formaldehyde by Rimini's colour reaction. After less than thirty minutes the degree of dissociation, if any, became evidently stable, and by matching the depth of blue colour obtained in the tests against previously standardised methylene blue solutions an approximate idea of the amount of free formaldehyde present at each acidity was obtained.

The results can be shown graphically as below.

It therefore appears that at an H-ion concentration of

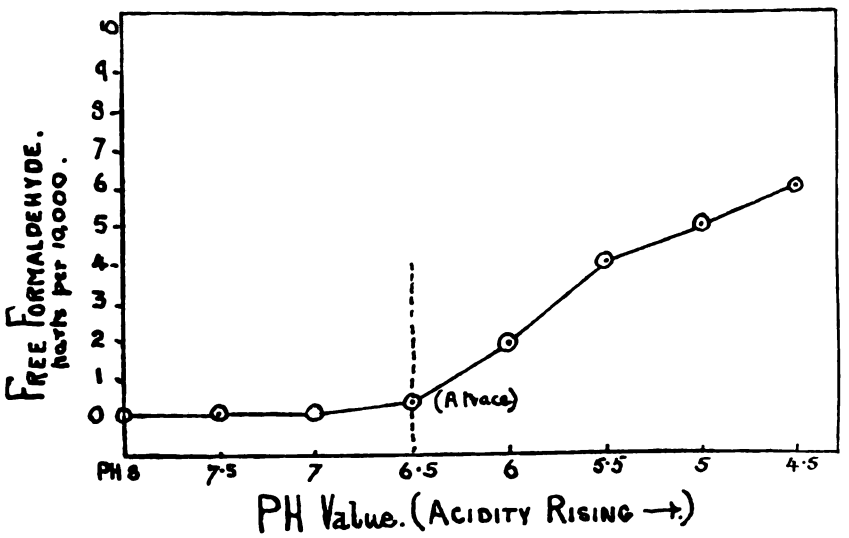

Fig. 1.

PH_6, a small but definite amount of free formaldehyde may be expected to exist in urotropine solutions, and that as the acidity rises this amount of dissociation gradually increases.

(2) *The Bacteria which Grow in Bile*

As a preliminary experiment also, it was considered necessary to test the suitability of human bile as a medium for the growth of commonly pathogenic bacteria. The bile, as for all these experiments, was obtained by aseptic aspiration of gall-bladders removed either at operation or from non-infected cases in the post-mortem room at Guy's Hospital.

Samples of whole bile which proved originally to be sterile

were tubed as ordinary culture media, the reaction was found in each case to be PH_7 to PH_8, the bile inoculated with a loopful of the organism concerned (24-hours' broth culture), and the tubes were incubated at blood heat for 48 hours. At intervals of 12 hours the tubes were shaken and from each a standard loopful was inoculated into about 5 c.c. of previously melted agar. After shaking, a plate was poured from the contents of each tube. The result of counting the colonies in these plates after further incubation gave a direct indication of multiplication, if any, of the organisms in the original bile. That given below is in no sense a complete list of those bacteria which will and will not grow in bile, but it seems to indicate clearly that whole bile from the gall-bladder is a favourable culture medium for many of the commonly encountered pathogenic organisms; a fact upon which, owing to the use of selective bile-salt media in bacteriology, occasional misconceptions have occurred.

Active multiplication in bile.
All strains of the *B. coli-B. typhosus* group.
Many strains of streptococci; two hæmolytic strains tested, both grew freely.
Some strains of staphylococci.

Weak multiplication in bile.
Remaining strains of strepto- and staphylo-cocci.
Some strains of *M. catarrhalis*.

Died out within 48 hours.
Pneumococci.
Most strains of *M. catarrhalis*.

(3) *Urotropine in Bile. Range of Bacterial Inhibition*

The foregoing experiment seems, therefore, to justify the use of whole bile as a medium in which to make bacteriological comparisons provided organisms of the first group are used, and the effects of adding known amounts of urotropine were next observed.

To a series of bile tubes pure urotropine was added in the strengths indicated. Each tube was inoculated with a standard loopful of the same broth culture of the organism in question, shaken and plates at once made as described in Experiment 2. Both bile tubes and plates were then further incubated at blood heat, and, from the former, further plates made at 24-hour intervals. The number of colonies in each series of plates was then taken to indicate the number of living bacteria per loopful of bile in the tubes.

TABLE A.

I. Each tube contained 3 c.c. bile + known amount of urotropine. Inoculated standard loopful of broth cultures 24 hours (*B. coli communis*). At 48 and 24 hours loopful removed and plates poured. Each + sign = approximately 20 colonies on these plates after 24 hours' incubation.

% of urotropine in bile.	Colonies at start.	After 24 hours.	After 48 hours.	Result.
2%	+++	±	0	Bacilli dead after 48 hrs.
1%	+++	+	0	do. do.
·5%	+++	++	0	do. do.
·25%	+++	+++	+	Marked inhibition
·1%	+++	++++	++	do. do.
·05%	+++	Strong growth	Strong growth	———
·025%	+++	do.	do.	———
Nil	+++	do.	do.	Control

II. Each tube contained 3 c.c. bile + known amount of urotropine. Inoculated with *B. typhosus* and treated as in previous table.

% of urotropine in bile.	Colonies at start.	After 24 hours.	After 48 hours.	Result.
2%	++	∓	0	Bacilli dead after 48 hrs.
1%	++	+	0	do. do.
·5%	++	+	0	do. do.
·25%	++	++	0	do. do.
·1%	++	+++	++	Marked inhibition
·05%	++	+++	++	do. do.
·025%	++	++++	Strong growth	? Slight do.
Nil	++	Strong growth	Strong growth	Control

Conclusion.—Against *B. coli communis*, (1) the lethal effect is seen with ·5% urotropine, (2) the inhibitory effect is seen with ·1% urotropine.
Against *B. typhosus*, the corresponding figures are about ·25% and ·05%.

The above are two typical results. The experiment was repeated several times, both with the same organisms and with streptococci, a definitely lethal effect at the end of 48 hours being observed in each case. The tables given are taken from average instances, because the end points naturally correspond to the resistance to antiseptics of the particular bacterial strain.

The sterility of those tubes marked 0 at 48 hours was very carefully confirmed by further sub-cultivation, and although it is not claimed that such figures for the number of living bacteria are more than a close approximate representation of those present in the tubes, yet it is submitted that there is no doubt that a germicidal effect does occur at the strengths of urotropine noted.

(4) *Gradual Lethal Effect in Bile*

The fact that complete killing of the bacteria did not occur until the lapse of so many hours led to a closer examination of the changes occurring within the bile.

Sterile whole bile containing 0·25 per cent. urotropine was placed in a closed tube, infected with one loopful of a 24-hour broth culture of *B. typhosus* and incubated continuously for 48 hours at blood heat. At intervals a little of the contents was aseptically removed and any increase of acidity noted with

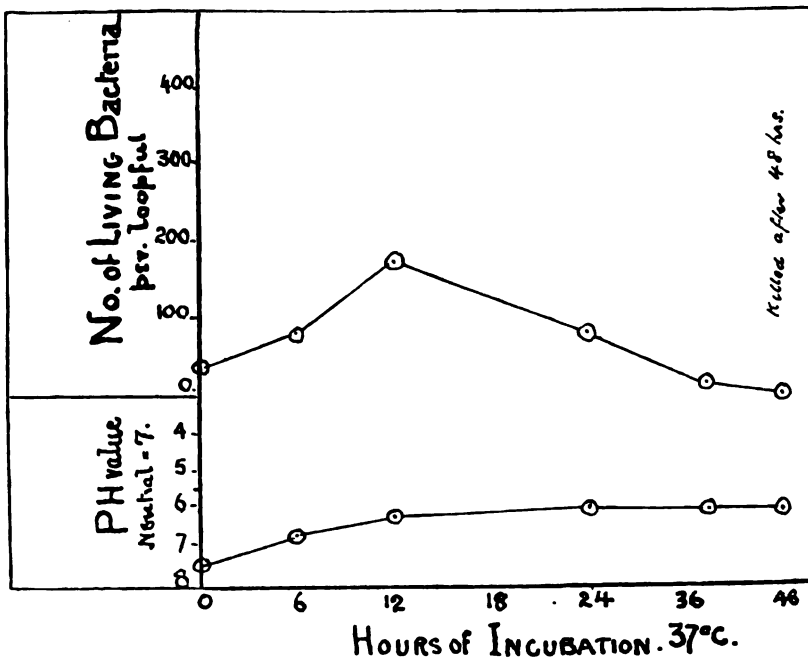

FIG. 2.

test papers. At the same time a standard loopful was plated as in the previous experiments. The result is best shown graphically as above.

It will be noted that there was evidently an initial multiplication of the bacteria followed by a definite rise in the acidity up to a point at which, from Experiment 1, a small amount of free formaldehyde might be expected to appear. Thereafter bacterial growth ceased and finally the organisms died out altogether. A control tube without urotropine was incubated and tested at the same time, and in this continuous growth occurred.

One explanation of these curves would be that the acid

formed by the growing bacteria in their immediate neighbourhood liberates formaldehyde from the surrounding urotropine. This process would lead first to their inhibition and ultimately to their death. In short, though urotropine has itself no antiseptic effect, the bacteria can themselves dissociate it until sufficient formaldehyde is liberated slowly to bring about their own death.

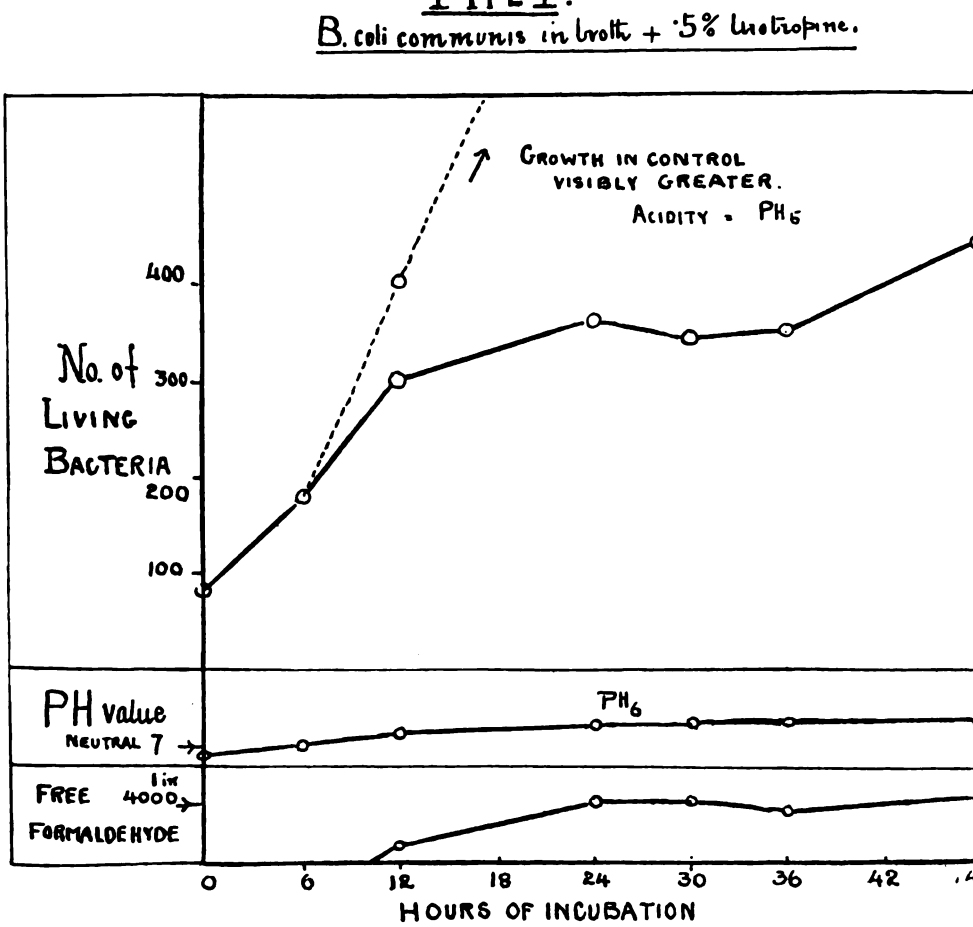

FIG. 3.

(5) *Urotropine Acting in Nutrient Broth*

The colour and opacity of whole bile making it a particularly difficult medium in which to perform colour reactions or to recognise macroscopical evidence of bacterial growth, the above theory was tested further, using nutrient broth instead of bile.

After sterilisation this broth was found to be $PH_{7.5}$ and to

contain ·2 per cent. glucose. As before, the medium was placed in closed tubes, these each inoculated with a loopful of some known broth culture, incubated at blood heat and at intervals tested for living bacteria. The PH value (B.D.H. indicator) and the presence of free formaldehyde by Rimini's colour reaction were determined at the same time. Control tubes of the same broth were inoculated with the same organisms.

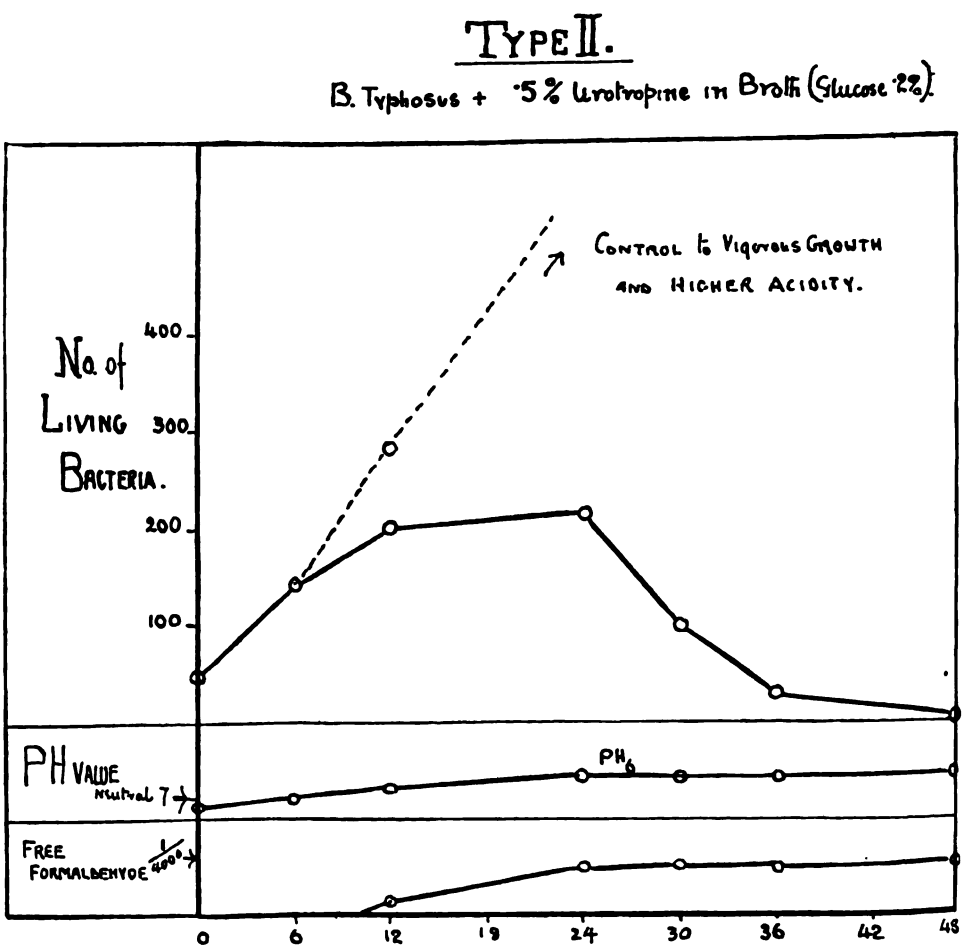

FIG. 4.

A number of such infected tubes were examined, using appropriate strengths of urotropine. The above results are given as typical of the curves obtained. Type 1 shows only a definite inhibitory tendency, and appeared when the initial infection of the tube was heavy, when a resistant bacterium was used or when the urotropine strength was too low. Type 2 resulted when there was a definite lethal effect within 48 hours.

In reading the curves it will be noted that the organisms grow rapidly at first, that the PH value rises at least to a point at which urotropine begins to dissociate, and that thereafter inhibition or actual death of the bacteria evidently begins.

To give quantitative results it may be said that for *B. typhosus* and streptococci of the longus type an inhibitory effect could be observed with ·1 per cent. to ·25 per cent. urotropine, and in very light infections this would probably be manifest in much greater dilution. For typical *B. coli communis* the corresponding figure, as seen above, is about ·25 per cent. to ·5 per cent.

In further support of the theory that this antiseptic action arises indirectly from local acid production, it must be mentioned that several attempts to obtain corresponding inhibitory effect in broth $PH_{7\cdot5}$ upon a non-acid producing coliform strain, *B. fæcalis alkaligenes*, failed in even 2 per cent. urotropine.

(6) *Urotropine in Cerebro-spinal Fluid*

At this point it must also be recorded that, having obtained working figures in the case of urotropinised broth, cerebro-spinal fluid (normal, faintly alkaline and glucose content ·2 per cent.) was substituted in the tubes of Experiment 5. To obtain a definite inhibitory effect, it was necessary to employ approximately the same strengths of urotropine as for faintly alkaline broth.

It will be seen that urotropine is in these experiments definitely more active in infected bile than in either cerebro-spinal fluid or broth. For example, one finds that in the latter 0·5 per cent. must be present to obtain complete killing of *B. typhosus* within 48 hours, whereas in bile 0·25 per cent. will achieve the same result. It appears that in bile some other factor must come into play, and the next experiment suggests that this factor is the action of the bile salts.

(7) *The Influence of Bile Salts*

To determine this a direct comparison was made between the germicidal power of formaldehyde alone and formaldehyde when mixed with the fluids under consideration. The Rideal-Walker technique for comparing antiseptics was employed, and the tabulated results were as follows :—

TABLE B.

A 24-hours' culture of *B. typhosus* used. Sub-cultures made at 2½-minute intervals, and these sub-cultures incubated for 48 hours at 37° C.

No.	Contents of original tube.	Mins.	Presence of growth in sub-cultures after intervals in minutes as below.									
		2½	5	7½	10	12½	15	17½	20	25	30	
1	0·1 Formalin (40% formaldehyde) 7·9 of saline alone = formaldehyde 1/200	+	+	+	+	+	+	+	+	0	0	*B. typhosus* killed in 25 mins.
2	0·1 Formalin + 7·9 of fresh bile	+	+	+	±	0	0	0	0	0	0	*B. typhosus* killed in 12½ mins.
3	0·1 Formalin in 7·9 fresh C.S.F.	+	+	+	+	+	+	−	+	0	0	*B. typhosus* killed in 25 mins.
4	Bile alone	+	+	+	+	+	+	+	+	+	+	Control

No.	Contents of original tube.	Mins.	Growth in sub-cultures after intervals.									
		2½	5	7½	10	12½	15	17½	20	25	30	
1	Formaldehyde 1/200 as above	+	+	+	+	+	+	+	+	0	0	*B. typhosus* killed in 25 mins.
2	0·1 Formalin + 7·9 solution of bile salts 1/100	+	+	+	+	±	0	0	0	0	0	*B. typhosus* killed in 15 mins.
3	Formaldehyde 1/200 + gram. 2 suspended cholesterin	+	+	+	+	+	+	+	+	0	0	*B. typhosus* killed in 25 mins.
4	Bile salts 1/100 alone	+	+	+	+	+	+	+	+	+	+	Control

Each tube (1–4) contained 8 c.c. of liquid. To each was added the same amount of a 24-hours' broth culture of *B. typhosus*. Loopfuls of the contents of the tubes were removed at 2½-minute intervals, and planted in broth tubes, subsequent incubation of which showed whether the organisms in the original tubes were alive at the time of removal. Results were read at the end of 48 hours.

Apparently the presence of bile salts directly accelerates the germicidal power of formaldehyde. In a 1 per cent. solution of bile salts formaldehyde (1/200) kills *B. typhosus* in 15 minutes, whereas the same strength formaldehyde alone requires 25 minutes. It is suggested, therefore, that herein lies the explanation of the more rapid antiseptic effect of urotropine when slightly dissociated in bile. The exact mechanism of the acceleration may possibly be connected with the marked lowering of surface tension which these salts are known to produce, but this, together with other points of detail which these few experiments raise, I hope to investigate further.

My sincere thanks are due to Dr. A. F. Hurst for his valued suggestions and to various assistants in the Clinical Research Association's Laboratories, who have aided in completing culture series and keeping records.

Conclusions

As to the clinical bearing of this note, it must at once be said that we need to know the exact quantities of urotropine which, in the living person, may be found in the bile. There seems to be no doubt that it is excreted by this route, and from comparative distillations of the bile obtained by a duodenal tube from the patients taking urotropine and samples of normal bile to which known amounts of the drug had been added, it appears that a concentration of 0·05 per cent, or even 0·1 per cent. might be readily attained if the patient takes the drug well.

From Table A it will be seen that in such circumstances a decided inhibitory or gradual lethal effect must be produced upon any bacteria present in the biliary passages. It appears certain, therefore, on experimental as well as clinical grounds, that urotropine has definite claims to be considered an active biliary antiseptic.

From past experience it seems unlikely that urotropine when administered by the mouth would ever be found in cerebro-spinal fluid in anything approaching the above quantities. Experiment 6 prompts the conclusion that the drug can, in this site, have nothing more than some very slight prophylactic value.

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THE DIAGNOSIS OF ADDISON'S (PERNICIOUS) ANÆMIA

Commentaries by ARTHUR F. HURST, M.D., Physician to Guy's Hospital, and by WILLIAM HUNTER, C.B., M.D., Consulting Physician to Charing Cross Hospital, on

TWO CASES OF SEVERE ANÆMIA

Reported by R. L. WATERFIELD and J. W. SHACKLE

INTRODUCTION

By ARTHUR F. HURST, M.D.

THE two cases recorded in this article are of great interest, as they raise the question as to what exactly constitutes Addison's (so-called "pernicious") anæmia. Can a diagnosis be made with certainty on the clinical evidence alone, or is post-mortem evidence required as confirmation? When the clinical evidence and the post-mortem evidence are conflicting, which is to be regarded as more reliable? And, lastly, what are the essential features of the clinical evidence and of the post-mortem evidence respectively?

Addison [1] would have diagnosed a case as an example of his "idiopathic anæmia" if a pale patient with a yellowish complexion and symptoms of anæmia, but of nothing else, died, and no sign of organic disease was found post mortem. Hæmatological, gastric and neurological investigations have amplified this simple conception, but at the same time difficulties have been introduced.

It is universally agreed that the anæmia is of a hæmolytic type, so that the lemon-yellow colour of the skin and the presence of excess of bilirubin in the blood but not in the urine, as shown by van den Bergh's test, are invariable symptoms, but they are not pathognomonic, as Addison's anæmia is not the only form of hæmolytic anæmia. Much has been written about the blood in Addison's anæmia, but most modern writers agree that the essential feature is the presence of megalocytes and microcytes (anisocytosis) and an increase in the average size of the red corpuscles. This subject has been worked out with mathematical accuracy by Price-Jones,[2] who believes that it is

possible to determine with certainty whether a case is one of Addison's anæmia or not by plotting a curve of the size of 500 accurately measured red corpuscles. A second hæmatological feature of great importance is the presence of megaloblasts; but this has a distinctly smaller value, as such cells are occasionally found in other anæmias and they may be absent for long periods in Addison's anæmia.

Investigations of the secretory functions of the stomach, especially by the fractional test-meal, have shown that complete achlorhydria is almost invariably, if not invariably, present from the earliest stages, and I have collected twelve cases in which it was known to exist from one to twelve years before the onset of anæmia. I doubt whether a diagnosis of Addison's anæmia can be justifiably made if free hydrochloric acid is found in the stomach.

The importance of a sore tongue, or a history of the tongue having been sore, is very great. Since William Hunter first described this symptom in 1890 it has gradually become recognised as occurring in at least 80 per cent. of cases, and it occurs very rarely in any other disease—not even the very similar hæmolytic anæmia caused by infection with Bothriocephalus latus—though I have recently observed it in three cases of secondary anæmia, which showed none of the other features of the Addisonian disease.

In about 80 per cent. of cases of Addison's anæmia symptoms or signs of subacute combined degeneration of the cord are present sooner or later. Bell and I [3] have shown reasons for believing that the association of these signs and symptoms with an anæmia is strong presumptive evidence that it is of the Addisonian type, and that, however slight the anæmia may be, achlorhydria is found to be present.

Thus from a clinical point of view a hæmolytic anæmia (shown by the lemon-yellow colour of the skin and a positive indirect van den Bergh's test) with great variability in size of red corpuscles and a large proportion of megalocytes, and with achlorhydria, especially if accompanied by a sore tongue or by signs or symptoms of subacute combined degeneration of the cord, may be regarded as conclusive evidence of Addison's anæmia.

From a pathological point of view the presence of hæmolysis, as shown by a positive Prussian-blue reaction in the liver, spleen, or kidneys, an increase in the red bone-marrow, and the absence of other evidence of disease are generally regarded as pointing to Addison's anæmia.

In Case 1 the clinical evidence was positive and the patho-

logical evidence negative; in Case 2 the clinical evidence was negative and the pathological evidence positive. Was either an example of Addison's anæmia? If the answer be in the affirmative, it will entail a revision of the summary I have just given of either the clinical or the pathological evidence required for the diagnosis of Addison's anæmia.

Case 1.—*Addison's Anæmia with Subacute Combined Degeneration of the Spinal Cord secondary to Cancer of the Stomach*

By R. L. WATERFIELD

A man, aged 52, was admitted into Addison Ward under Dr. A. F. Hurst on August 3, 1922, for progressive weakness in the legs and arms, and pains in chest and abdomen. In October 1921 he had begun to have a sensation of pins and needles in his hands and forearms, and he found the muscles of his limbs were getting weak. In December he began to get indigestion with eructation and pain from one and a half to two hours after meals. The pain was partially relieved by food, and extended over the whole of the abdomen and chest. The bowels at this time acted normally. He vomited occasionally and twice noticed a little blood in the vomited material.

In June 1922 the weakness and "pins and needles," which had been almost confined to the upper limbs, now appeared in his feet and legs. There was also some unsteadiness in walking. He found that exertion gave him pain over the region of his heart and made him short of breath. Between June and his admission in August his weakness became more marked and for some months he steadily lost weight. Since March 1922 his tongue had been painful and ulcerated.

On admission the patient's complexion was a pale lemon-yellow colour. His cranial nerves showed no abnormality. His knee-jerks and ankle-jerks were normal and equal; the plantar reflexes were extensor. The abdominal reflexes were difficult to obtain. Vibration sense was absent in the left leg and diminished in the right. The "shooting test" was performed badly with the right fingers and left toes. There was no astereognosis. The patient could differentiate hot from cold tubes, but pin-pricks and the touch of a blunt object on the fingers seemed to him the same. He was able to appreciate the touch of cotton-wool everywhere except on the soles of his feet. His muscles were flabby and feeble, but his grip was fairly strong. The blood and the cerebro-spinal fluid gave a negative Wassermann reaction, and the latter contained no excess of cells.

His tongue was fissured and sore, and several small ulcers were present. His teeth were very septic, and there was universal severe pyorrhœa alveolaris. The tonsils were normal.

A fractional test-meal showed complete achlorhydria with

blood, pus and mucus in each specimen; the gastric contents had a very foul smell. The x-rays showed a hypertonic rapidly emptying stomach with no irregularity in outline suggestive of cancer. The fæces gave a strong guaiac test and a well-marked hæmatoporphyrin spectrum. A doubtful tumour was felt high up in the epigastrium. The spleen was enlarged and firm. The liver was slightly enlarged. The urine was dark in colour, and contained no abnormal constituents. The bowels were regular. The systolic blood pressure was 88 mm. Hg., and the diastolic 55 mm. Hg. The heart appeared to be normal.

The following table shows the number of red and white corpuscles, hæmoglobin percentage and colour-index at different dates.

Date.	Hæmoglobin percentage.	Red Cells, per cub. mm.	Colour-Index.	White Cells, per cub. mm.
14.9.22	31	1,500,000	1·03	4,700
18.9.22	24	—	—	—
20.9.22 *	30	1,250,000	1·2	5,330
25.9.22 *	32	—	—	—
29.9.22	20	1,200,000	0·83	4,675
30.9.22	36	—	—	—
5.10.22	20	—	—	—
19.10.22	30	1,300,000	1·15	—
21.10.22	28	—	—	—
	25	—	—	—
23.10.22 *	36	—	—	—
	35	1,500,000	1·16	—

* After transfusion.

On October 9 Dr. Cecil Price-Jones reported that the blood film presented the typical picture of Addison's anæmia. A transfusion was performed on September 18 and 23 and on October 21.

A diagnosis of subacute combined degeneration of the cord with Addison's anæmia, and hæmorrhagic gastritis, or possibly carcinoma of the stomach, was made. As no improvement followed removal of the septic foci in the mouth, the administration of hydrochloric acid and arsenic, and transfusion repeated on two occasions, Mr. R. P. Rowlands was asked to operate on October 24 in order to remove the spleen, if no growth was found. A large inoperable neoplasm was, however, discovered in the cardiac half of the stomach with large and hard glands near the lesser curvature. Pus was in the peritoneal cavity. The patient died ten days later.

At the post-mortem the tongue was ulcerated in its posterior part. The pericardium was very pale and bright yellow in colour. The heart was surrounded by a great deal of bright yellow fat. The stomach showed a large fungating mass occupying more than half of the mucous surface. Many hard nodular glands were found on the greater and lesser curvature.

The liver showed one nodular lump on its surface, and the pancreas contained several secondary deposits. The spleen was soft and enlarged, 18 cms. long, with its capsule thickened. The ribs on section showed an extraordinary development of the red-marrow. None of the viscera gave a definite Prussian-blue reaction. Dr. C. P. Symonds found the typical changes of subacute combined degeneration in the spinal cord.

COMMENTARY BY ARTHUR F. HURST, M.D.

Clinically there seemed no doubt that this was a case of Addison's anæmia. The patient had the characteristic lemon-yellow colour, his blood picture was typical, he had the sore tongue described by Hunter, van den Bergh's test gave an indirect positive reaction, complete achlorhydria was present, and he showed well-marked symptoms and signs of subacute combined degeneration of the spinal cord. The only unusual feature of the case was the presence of a considerable quantity of blood in each fraction of the test-meal on both occasions on which one was given. I have never before seen such an occurrence in Addison's anæmia. One possible explanation was that the chronic gastritis which is frequently associated with the achlorhydria had taken on an acuter hæmorrhagic form. Another possibility was that this case was an example of the condition which J. R. Bell and I had been led to anticipate might occur from our investigations on the pathogenesis of subacute combined degeneration of the cord, the results of which were about to be published in *Brain*[3] at the moment when this patient came under my observation. We had shown that this disease appears to be always associated with achlorhydria, which we regarded as the essential predisposing cause both of the nervous degeneration and of the Addisonian anæmia which probably always accompanies it. We had failed to discover any report of an actual case of cancer of the stomach associated with subacute combined degeneration of the cord, although several writers had referred to the occurrence of such an association as an alternative to the more common one with Addison's anæmia. We suggested that, should future observations definitely prove the existence of this association, it would probably be found only to occur among the 50 per cent. of cases of cancer of the stomach in which complete achlorhydria is present throughout the period of digestion. We had shown that the achlorhydria of Addison's anæmia and subacute combined degeneration of the cord is not the result of any specific gastric disease, as it might result from a variety of

causes; there is no reason why cancer of the stomach should not be one of these.

In this case the presence of a severe anæmia was as obvious as that of subacute combined degeneration of the cord, and the anæmia was certainly of the Addisonian type, and not of the secondary type commonly seen in cancer of the stomach. There is no reason why the presence of cancer of the stomach should exclude the possibility of Addison's anæmia being also present, and the discovery of a growth of the stomach at the exploratory operation and its confirmation after death in a patient with Addison's anæmia and subacute combined degeneration of the cord simply confirms what we had regarded from purely theoretical considerations as a rare but quite possible association.

The absence of a definite Prussian-blue reaction in the viscera after death has often been observed before in cases in which the neurotoxin has been more active than the hæmolysin, as its presence indicates the deposition of iron in moderately large quantities over a period of some duration. In this case the total duration of the disease was probably just over a year, and the first symptoms of anæmia only appeared five months before death.

It will in the future be of great interest to examine the blood of patients with inoperable cancer of the stomach in order to see how often during the last stage an Addisonian type of anæmia is added to the earlier secondary anæmia, whether this only occurs when achlorhydria is present, and whether under these conditions any signs or symptoms of subacute combined degeneration of the cord can be discovered. It is only natural that both the anæmia and nerve signs should escape observation in a large majority of cases, as when the diagnosis of inoperable cancer has once been made it is not likely that careful hæmatological and neurological investigations will continue to be made.

Case 2.—*Fatal case of "Idiopathic" Hæmolytic Anæmia with Normal-sized Red Corpuscles and without Achlorhydria*

By J. W. SHACKLE

Ellen C., aged 61, was admitted into Guy's Hospital under Dr. A. F. Hurst on October 13, 1922. She had had no previous diseases of note, and had never been abroad. She gave a history of frequent epistaxis and numbness of the hands some years ago on waking. Both troubles disappeared and had not since recurred. During the last two years she had lost some weight.

Three months before admission she had transient deafness associated with a cold, and about the same time she became unable to walk even a short distance owing to increasing general weakness and shortness of breath. After a time the least exertion caused acute breathlessness and palpitation. She also had severe headaches of varying intensity and duration, together with giddiness, on waking in the morning. Two months before admission she noticed that she was beginning to appear yellow. She also noticed that she no longer bled readily.

On admission she was very weak and appeared cachectic. She was very pale and had a definitely lemon-yellow colour,

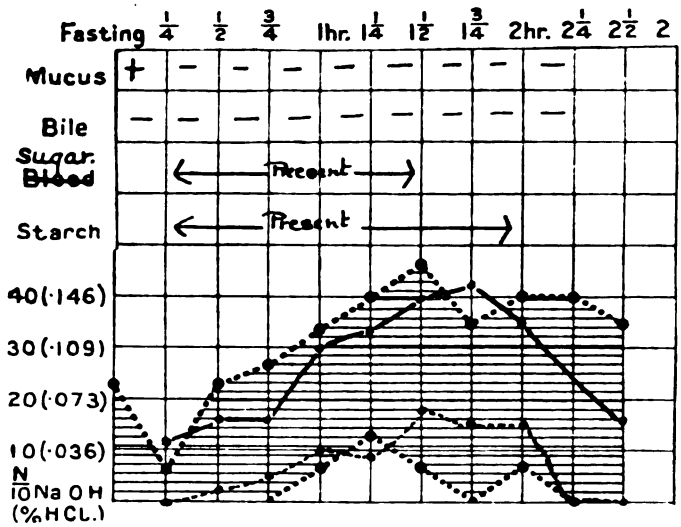

FIG. 1.

Shaded area = limits of free HCl in 80 per cent. of normal people. Continuous line = total acidity. Dotted line = free HCl.

which became more obvious the last few days of her life. The hæmoglobin percentage was 44, the red cells numbered 1,769,000 per cub. mm., the colour-index being 1·24. The leucocytes numbered 7,875 per cub. mm., and of these 78·7 per cent. were polymorphonuclear, 18·3 per cent. lymphocytes, 2 per cent. hyaline and 1 per cent. eosinophile cells. There was no anisocytosis and no nucleated red cells were seen, but poikilocytosis was present. There was a marked "water-hammer" pulse; the systolic blood pressure was 145 mm. Hg., and the diastolic 65 mm. Hg., but the heart sounds were quite normal, and the heart not dilated.

The tongue was clean and moist and had never been sore. The tonsils were not inflamed or enlarged; the teeth were carious, and there was marked pyorrhœa. There were no digestive symptoms and the patient's appetite had been good

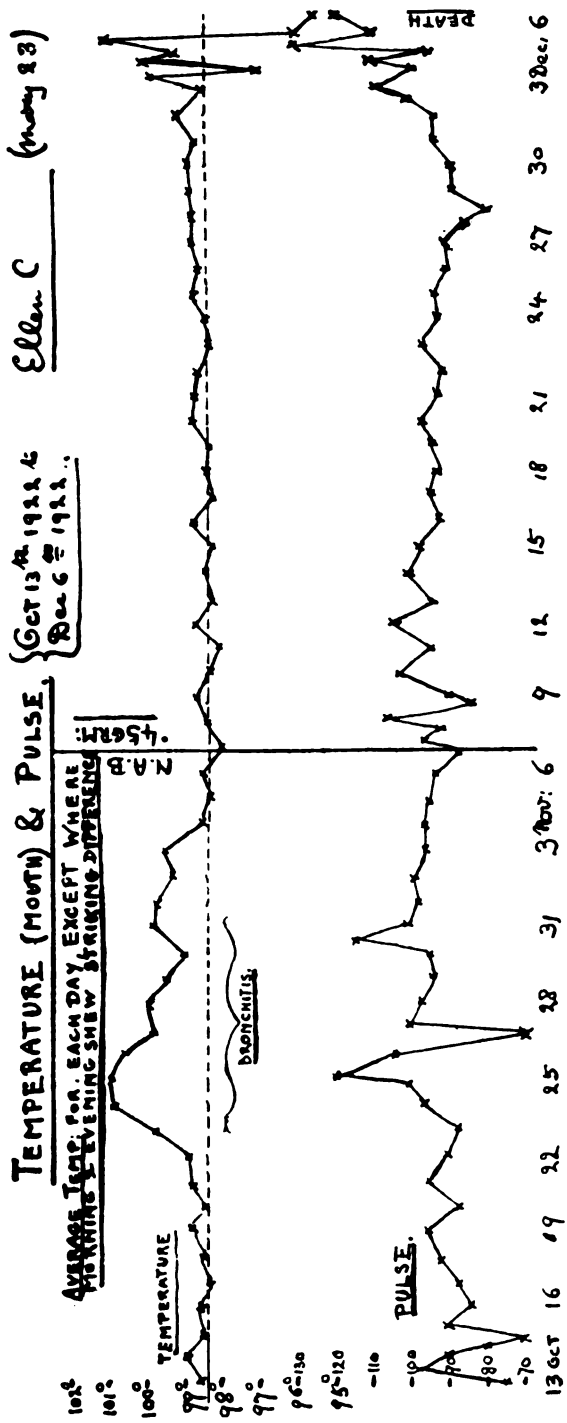
TEMPERATURE (MOUTH) & PULSE.
Ellen C
(Nursery 23)
Oct 13th 1922 to Dec 6th 1922.
AVERAGE TEMP. FOR EACH DAY EXCEPT WHERE MORNING & EVENING SHEW STRIKING DIFFERENCE
A.M.
P.M.
TEMPERATURE
BRONCHITIS
PULSE.
DEATH
13 Oct 16 19 22 25 28 31 3 Nov 6 9 12 15 18 21 24 27 30 3 Dec 6

FIG. 2.

till a week before admission; the bowels were perfectly regular, the stools being always normal in colour. The abdominal wall was found to be lax, and the liver, spleen, both kidneys and stomach were unusually low. The liver and spleen seemed somewhat enlarged. A test-meal showed the presence of free hydrochloric acid in the stomach (Fig. 1). No irregularity of outline of the stomach or gastric delay was detected in the x-ray examinations. The guaiac test for occult blood in the

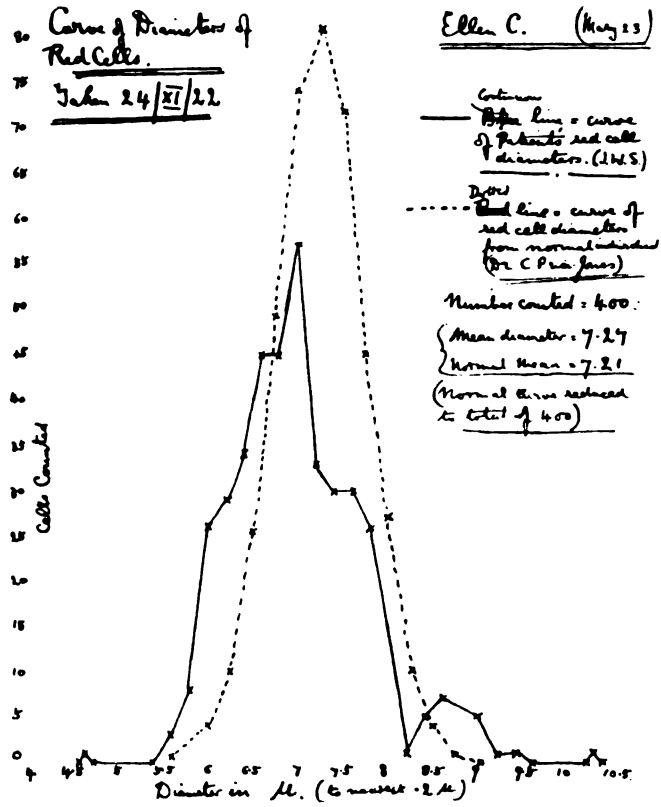

FIG. 3.

fæces was weakly positive; much pigment was present, but no definite blood spectrum. Mr. J. H. Ryffel concluded that there was no evidence of bleeding. There was no evidence or history of intestinal worms. The urine was normal.

The reflexes were normal, and there was no sign of degeneration of the central nervous system. No retinal abnormality was observed. The Wassermann reaction was negative.

Hyman van den Bergh's test for excess of bile pigment in the blood gave a negative direct reaction and a positive indirect one, indicating an excess caused by blood destruction and not biliary obstruction.

The temperature on admission was 98·8°, but from October 21 to November 4 the patient had marked pyrexia, the temperature rising on October 25 to 102°. On November 30 a second bout of pyrexia developed which lasted till death on December 6 (Fig. 2).

On November 24 a red cell-diameter estimation was made.

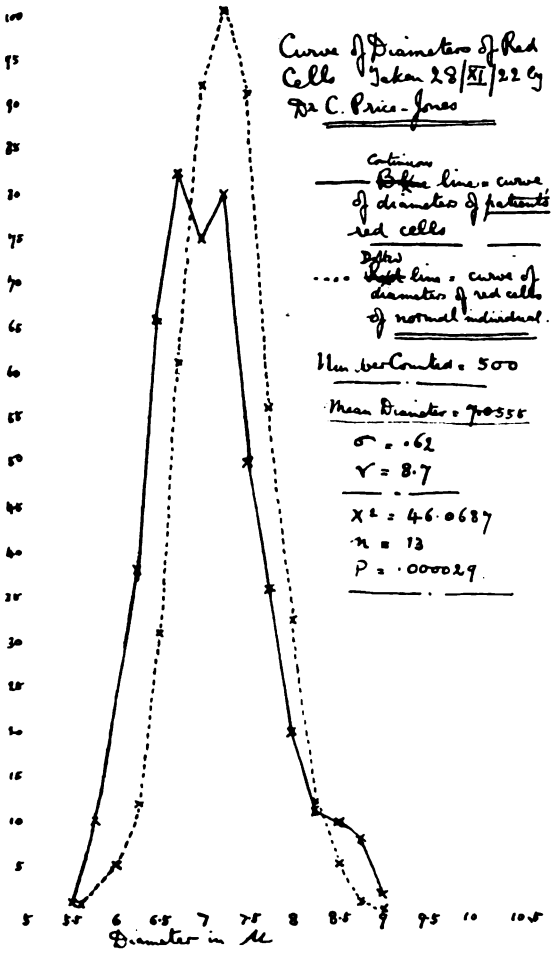

FIG. 4.

The curve obtained by this method was typical of a secondary anæmia (Fig. 3). Another estimation was carried out on November 28 by Dr. Cecil Price-Jones; he obtained a similar type of curve (Fig. 4). He reported that, though the high colour-index might at first give rise to a suspicion of Addison's anæmia, he regarded the case as quite definitely one of a secondary or cachectic anæmia, as the cell-diameter curve was typical of the latter, showing no increase in the average size of red corpuscles and no anisocytosis.

The patient showed no sign of improvement and died on December 6, 1922. The following table compiled from the full table of blood counts gives a summary of the blood condition of the patient while in the hospital.

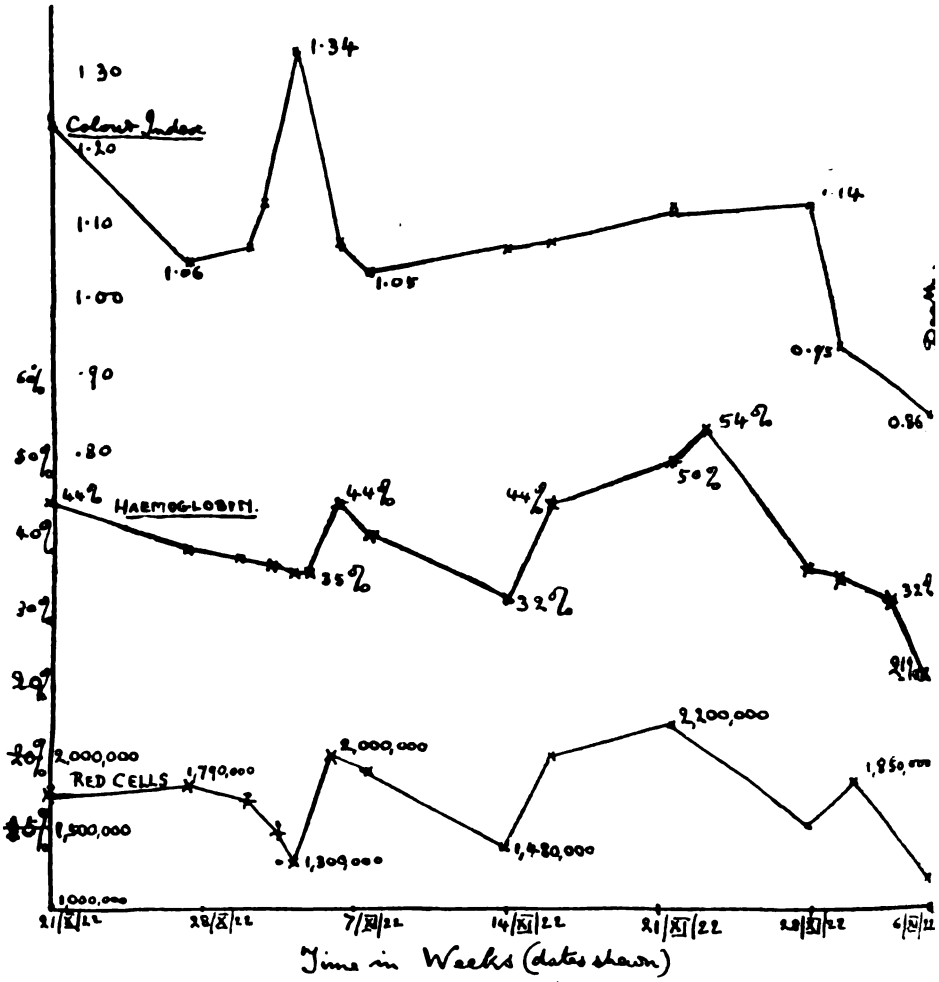

FIG. 5.

Date.	Hæmoglobin percentages.	Red Cells, per cub. mm.	Colour-Index.	White Cells, per cub. mm.
21.10.22	44	1,769,000	1·24	7,875
3.11.22	35	1,300,000	1·35	8,750
6.11.22	44	2,050,000	1·09	4,845
22.11.22	50	2,220,000	1·13	4,830
28.11.22 *	36	1,640,000	1·12	9,355
30.11.22	35	1,850,000	0·95	12,825
5.12.22	21	1,224,000	0·86	19,220

* Count by Dr. R. D. Passey.

A graph of the hæmoglobin, red cells and colour-index for the complete period is given in Fig. 5.

Throughout there was considerable irregularity in the shape of the red cells; normoblasts were seen on only three occasions, and megaloblasts never.

The post-mortem examination revealed no neoplasm or septic focus of any kind. The heart showed evidence of fatty degeneration, but no signs of endocarditis. The liver was somewhat enlarged; both the liver and the kidneys gave the Prussian-blue reaction, though somewhat slowly. The spleen was slightly enlarged and was soft in consistency. When opened aseptically several soft pulpy degenerated areas were found; these were sterile on cultivation, and were considered by Prof. Adrian Stokes and Dr. F. W. Nicholson to be infarcts.

The bone marrow of the humerus was found to be converted into the "red currant jelly" type. A smear from it showed that the normal fat cells were largely replaced by masses of cells, a large percentage of which were normoblasts, there being also numerous neutrophil and eosinophil myelocytes.

Commentary by Arthur F. Hurst, M.D.

The colour of the skin, which was definitely lemon-yellow during the last few days of life, the positive indirect van den Bergh's reaction, and the Prussian-blue staining of the liver and kidneys post mortem, prove that the anæmia from which this patient died was hæmolytic in origin. As no other cause of death was found and the red marrow was greatly hypertrophied, the post-mortem examination would certainly point to Addison's anæmia as the diagnosis. But although the colour-index of the blood was high, the size of the red corpuscles, when accurately measured on two different occasions, differed so fundamentally from what Dr. Cecil Price-Jones has always found in Addison's anæmia that he came to the conclusion that the anæmia was undoubtedly not Addisonian. The constant absence of megaloblasts and the discovery of a very few normoblasts in only two of the numerous films examined pointed in the same direction. If the presence of hydrochloric acid in the gastric contents had been the only evidence against Addison's anæmia, it might have been regarded as proving that the rule that achlorhydria is always present is not absolute but has very rare exceptions. When, however, it is associated with a blood-picture which definitely excludes Addison's anæmia, it can certainly be regarded as an additional strong argument against that diagnosis. The same may be said about the absence of soreness of the tongue and of nervous symptoms, though, as these are not present in more than about 80 per cent. of cases, neither by itself would be of great importance.

The unusually high pyrexia and terminal leucocytosis suggest the probability that the anæmia might have been secondary to a hæmolytic streptococcal septicæmia, which would lead to post-mortem changes indistinguishable from those of Addison's anæmia. The case would then fall into the group of cases described by Hunter as "septic anæmia," a condition which he regards as quite distinct from Addison's anæmia.

Commentary by William Hunter, C.B., M.D., Consulting Physician to Charing Cross Hospital

I am indebted to Dr. Hurst for giving me an opportunity of studying the two interesting cases of severe anæmia he has recorded, and I gladly comply with his request for my opinion as to their character.

They raise the question so much discussed as to the individuality and identity of the disease historically known as "Addison's Idiopathic Anæmia," or "Addisonian Anæmia," and generally known as "Pernicious Anæmia," and how far its features are distinctive enough to enable it to be identified even if associated with cancer of the stomach (Case 1) or simulated by other anæmias (Case 2).

The question involved in Case 1 is as to the presence of this type of anæmia—Addison's idiopathic anæmia. If it was present, what was its relationship to the cancer of the stomach—did it precede or follow it? If it preceded the cancer, it could not be regarded as "secondary" to the cancer. If it followed the cancer—was "secondary" to it—it could not be regarded as Addison's anæmia, "this very remarkable disease," as Addison originally, and in my judgment correctly, termed it; this very remarkable and specific infective disease, as my studies (1885–1922) reveal it to me.

In view of its nature, I have carefully considered the facts recorded, as also those of Case 2. I have done so in the light of my studies and experience of 200 cases of Addisonian anæmia, including 29 post-mortems; and of many cases of the severe anæmia which most resembles it—"septic anæmia," as I term it, including 30 post-mortems.

Diagnostic Features of Addison's Anæmia

The particular infective lesion which I find most distinctive, most easily recognised, and most helpful in diagnosis, is the *history* or *presence* of a peculiar sore tongue, found in every one of my total series of 200 cases of Addisonian anæmia, and not

found in any other anæmia, as I have recently described (" Pernicious Anæmia " and " Septic Anæmia," *Brit. Med. Journ.*, March 1922).

Its value in diagnosis in individual cases may be illustrated by the following case, seen 1912 :

A lady aged 68, blood report showed red cells 49 per cent., hæmoglobin 56 per cent., colour-index 1·2, leucocytes 5000. The provisional diagnosis of this report was : " This blood picture might agree with that of pernicious anæmia."

On inquiry it was at once ascertained, " Her mouth has been sore for the last eight months; unable to take hot drinks; is now sore more or less all the time." This history is characteristic of what I find in varying degree in all cases.

The particular clinical features which characterise the disease are those of : (*a*) intermittent glossitic, gastric, or intestinal symptoms (the gastric features including achlorhydria, which I have always found present in any case I have examined since 1900 as an interesting feature of the disease); (*b*) increased blood destruction, varying from time to time and shown by varying colour of the urine (hæmolytic features); and (*c*) nervous features of various kinds—peripheral, cerebral, cord. The latter may take the form of subacute combined degeneration (present in 13 out of my series of 200 cases—or about 7 per cent.). I have never found this condition in any case of anæmia that had not at one time or other presented the glossitic and hæmolytic features and course of Addisonian anæmia.

The clinical features as a whole are thus those of " a glossitic, hæmolytic, neuropathic disease," as recently described and defined by me (" Nervous and Mental Disorders in Severe Anæmias," *Proc. Roy. Soc. Med.*, November 1922), and illustrated by two cases recording the full relations of these features to each other.

The particular post-mortem features which distinguish it include :

(*a*) The presence of definite infective lesions in the tongue, stomach, or intestine; I have found them in all cases when looked for in the tongue by careful histological examination (*e. g.* in 20 out of 29 post-mortems made in my cases).

(*b*) The presence of excess of pigment in the liver as determined *not merely* by degree of iron reaction of pieces of the organ tested by sulphide of ammonium or the Prussian-blue test at the post-mortem (a test which in doubtful cases can be misleading); but by histological examination and by chemical analyses, *e. g.* an average of 0·393 gramme per cent. of dried residue of the liver in 25 of my cases; as compared with 0·080 in health; 0·066 in 20 cases of severe " septic anæmia " and other septic conditions; and 0·026 in four cases of cancer of the stomach.

(*c*) The presence of marked hyperplastic changes in the bone marrow.

Lastly, in diagnosis, the particular feature I find most distinctive of the disease is the history or presence of sore tongue, found in all my series of 200 cases.

The anæmias which most closely resemble each other are:

(A) Addisonian anæmia (seasonal, *glossitic*, hæmolytic, hyperplastic).

(B) "Septic Anæmia," Hunter, 1900–8 (*non-glossitic*, non-hæmolytic, aplastic).

(C) Cancer of stomach (*non-glossitic*, non-hæmolytic, aplastic).

(D) Bothriocephalus anæmia (*non-glossitic*, hæmolytic).

Nature of Cases Reported

The foregoing, according to my studies, being the distinguishing features of the chief types of anæmia, the nature of the cases now recorded is the following:

Case 1.—This was a case of Addisonian anæmia (A), presenting the glossitic, hæmolytic and neuropathic features, which in my observation distinguish that disease—the most distinguishing feature being the presence of its sore tongue. The disease existed in October 1921, a year before his death, as shown by presence of nervous features; probably also for some time previous to that date.

It was accompanied by a definite degree—possibly a high degree—of "septic anæmia" (B) caused by the marked oral sepsis present in the case ("the teeth were very septic, and there was severe pyorrhœa").

As a pure clinical coincidence, cancer of the stomach (C) developed in the same patient—subsequent to the presence of the Addisonian anæmia (A). This was followed in due course by a still more severe degree of "septic anæmia" (B), when the extensive sloughing set in ("large fungating mass occupying more than half of the mucous surface"). The patient was thus in the grip not only of his original Addisonian hæmolytic disease (A), but of septic anæmia (B) of an unusually severe character, caused not only by the severe oral sepsis which he originally had, but still more by the intense septic ulceration of his cancerous growth. To these two were added the degree of anæmia associated with the presence of the cancer itself (C); this degree is very slight when no septic ulceration is present (*e. g.* 80 per cent. of red cells); but becomes marked when septic ulceration with septic anæmia (B) is superadded (*e. g.* 40 per cent. of red cells).

The post-mortem findings showed the hyperplastic marrow changes ("an extraordinary development") characteristic of the Addisonian hæmolytic disease (A); and characteristically absent in septic anæmia (B); and in cancer (C).

The excess of iron usually found in the liver and kidney in Addisonian anæmia (A) was not found in the case (" none of the viscera gave a definite Prussian-blue reaction ").

The exact significance to be attached to words like " no definite reaction," or " a reaction, though somewhat delayed," in connection with the amount of iron present in the liver when tested macroscopically, is, in my experience, often open to doubt. I have never relied on such examinations in the course of my studies, as affording conclusive information as to the amount of iron present. From 1888, when I first described the pathological and diagnostic importance of this change, I stated that the test was not the naked-eye test on pieces of the organ (by sulphide of ammonium or the Prussian-blue test), but the presence of excess of pigment, as shown by microscopic examination, and the application of the Prussian-blue test to such sections. Nearly every liver will give some degree or other of blue reaction to the HCl ferrocyanide of potassium (Prussian-blue test)—the colour deepening according to the time the piece of organ is left in the solution, exposed to the strength and disintegrating action of the HCl used. I have, therefore, in all my cases controlled my observations by having actual chemical analyses made of the three organs—liver, kidney and spleen. The result has been oftentimes surprising, in both directions, revealing in some cases a percentage of iron in the organs far in excess of the amount apparently present as judged by testing in the P.-M. room, revealing in others an amount less than the reaction in bulk appeared to suggest.

In the present case the absence of any such definite reaction, and presumably of any excess of iron in the organs, might well be accounted for by the extraordinary degree of septic anæmia (B) present in the case, conjoined with the presence of cancer (C). As my analyses show, both these anæmias are characterised by a great drain on the iron of the body, and by a corresponding great fall in the percentage of iron in the organs (especially in the liver, *e. g.* from the normal 0·080 in health, to 0·066 in septic anæmia (B); and still lower figures 0·026 in cancer of the stomach (C)). I am not disposed, therefore, to attach any undue importance to the absence of the usual change in this case. For the case, in the combination of two diseases in the one patient, was itself unusual. The most remarkable feature about it indeed is, that the features of the Addisonian anæmic disease (A) were not more overwhelmed or obscured in character by their association with so grave a condition as cancer of the stomach (C).

The chief outstanding characteristic clinical features of this glossitic hæmolytic and nervous disease (A) were present in their entirety—the nervous features including those of sub-

acute combined degeneration of the cord. As I have recently shown, I have only met with this latter in 7 per cent. of a total of 200 of my cases (not in 80 per cent. as Dr. Hurst says is his experience). Moreover, I have never met with it in any case of anæmia which had not at one time or another presented the clinical features of glossitis and hæmolysis, and the clinical course which I have found in every case of Addisonian anæmia I have seen, and which I have never met with in any other anæmia or any other disease. In particular I have never met with or heard of the nervous features, least of all subacute combined degeneration of the cord, in any case of cancer of the stomach.

Lastly, the blood picture presented by the case was that of Addisonian anæmia, with its colour-index above normal (present in my cases in 80 per cent. of all counts), and its leucopenia. It was not that of cancer of the stomach, which in my experience has always a colour-index much below the normal (0·5), and generally a marked leucocytosis caused by the septic ulceration of the growth.

The case, therefore, seems to me to have originally been one of Addisonian anæmia (A) existing for at least a year, possibly a year and a half or more, pursuing a mild and subacute course, and showing a high degree of compensatory marrow changes. By coincidence a cancer of the stomach developed in the same case. If this had existed before the development of the Addisonian anæmia (A), it is hardly likely that the marrow would have undergone such an intense hypertrophy. The existence of this hypertrophy seems to be strong evidence that the Addisonian anæmia existed prior to the development of the cancer.

The case might be entitled one of Addisonian anæmia *associated with* cancer of the stomach. It was certainly not secondary to the cancer.

Case 2.—This requires briefer consideration, although it is itself interesting. It represents a type of case far more common than Case 1—and one that gives the greatest difficulty in diagnosis. It illustrates the extraordinary diagnostic value likewise which I have attached to sore tongue in Addisonian anæmia. The absence of sore tongue showed that it was not Addison's anæmia (A).

The mode of onset, the existence of hæmorrhages, the character of the blood changes, the "normal" character of the urine and stools, and the existence of marked septic lesions (carious teeth and marked pyorrhœa) are features characteristic of the anæmia I term "septic anæmia" (B)—non-glossitic and non-hæmolytic.

"The liver and kidney gave the Prussian-blue reaction, though somewhat slowly." That is to say, the excess of iron if any was but slight. "The bone marrow of the humerus was converted into the 'red currant jelly' type, made up chiefly of normoblasts." That is to say, the marrow change in this case, like "red currant jelly," conveys to me something different from that found in Case 1 and described as "an extraordinary development"—generally marked, although no data on this point are given, by the presence not only of large numbers of normoblasts, but also of megaloblasts and other kinds of marrow cells.

I find that the infection underlying this class of anæmia (B) is in all cases largely streptococcal; but cases of septic anæmia (B) are sometimes complicated by other kinds of infection responsible for some degree of hæmolysis that may characterise them. This hæmolysis gives them their apparent resemblances to the Addisonian type of anæmia (A). It is usually slight and is not reflected in the general character of the blood changes, which are most frequently those of septic anæmia (B). But they may be reflected in the higher colour-index presented by such cases (*e. g.* Case 2); and also sometimes by increase of iron in the liver (*e. g.* 0·110 and 0·230 per cent. in two of my cases of malignant endocarditis and calculous pyonephrosis respectively).

Lastly, this group is characterised by most varying leucocyte changes—sometimes low, sometimes high (as also shown in Case 2, in which the leucocytes varied between 4,800 and 19,200 per c.cm., and stood at the latter number at death).

My conclusion about Case 2, therefore, is that it was not of the nature of the "idiopathic anæmia of Addison," "idiopathic hæmolytic anæmia" (A). To apply the latter title—"idiopathic hæmolytic anæmia"—the title which connotes the idiopathic nature and hæmolytic character of Addison's anæmia—would therefore be misleading.

The title under which I should describe such a case would be: "A Fatal Case of 'Septic Anæmia' of Mixed Infective Character."

The two cases are thus crucial ones as regards the identity of Addison's anæmia (A), and the possibility of recognising it even when associated with any other disease. In expressing my opinion I have not had the advantage of observing the cases clinically during life, or of making the pathological observations at the post-mortem, and the detailed histological studies and chemical analyses of the liver, kidney and spleen for iron, which I am accustomed to make in all my cases of anæmia. As regards the relative value of clinical and post-mortem observations in the diagnosis of cases of anæmia of doubtful nature, there is in my experience no doubt. For purposes of diagnosis

I would rather see a case of severe anæmia during life than base my diagnosis on any blood changes or other features that might be presented in the form of reports. My experience is that the infective and clinical features of severe anæmias ascertainable at the bedside go deeper into their nature and help more in their diagnosis than any other class of observation connected with the case—useful and informing as many of these latter may in many cases be. In my total of 200 cases of this disease, I find that the cases whose nature I have had difficulty in deciding are only seven in number, and these are cases which I did not see either during life or at the post-mortems.

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THE ETIOLOGY AND TREATMENT OF VARICOSE VEINS

By PHILIP TURNER, M.S., Surgeon to Guy's Hospital.

VARICOSITY of the veins of the lower extremity is an important condition, partly on account of its frequency, and partly on account of the severe and disabling complications, such as ulceration, dermatitis, chronic œdema, phlebitis and thrombosis, which are likely to appear in advanced stages of the disease. In a great proportion of the cases in which these complications are present the trouble is so advanced that real cure is impossible, and in many palliative measures can only afford a moderate degree of relief. As they occur chiefly in old-standing and often neglected cases, it is clearly desirable that curative measures should be carried out in the early stages of the disease before they appear.

The obvious nature of the trouble, the tedious character of the operations usually employed, and the frequency of indifferent results after operative treatment have led to varicose veins being regarded as a dull and uninteresting subject, so that our knowledge of the pathology and the treatment is much the same as when Sir William Bennett wrote his monograph some thirty years ago.

The operative treatment, usually by one of the methods of excision, is not particularly satisfactory, though excision of localised varices in young adults is often successful; yet in many cases, especially where the patients are older and the disease is more advanced, there is rapid recurrence of varicosity, either at the site of operation or elsewhere.

ETIOLOGY

As a general rule, both for the prevention of a disease and for efficient treatment when it has appeared, it is necessary to know something of its etiology. Our knowledge of the cause of varicose veins is not altogether satisfactory. The trouble is very common, occurring in all classes, affecting both men and women, and in those following both sedentary and active occupations. It is generally agreed that the essential factor is an increase of pressure in the veins, occasionally due to some easily recognised obstruction to the flow of blood. Such are pregnancy, pressure by tumours, abnormal communications between arteries and veins, thrombosis of the femoral vein, and after an injury such as a fracture of the pelvis. In another group the varicosity is vaguely attributed to a congenital

defect or abnormality of the veins: rarely they are part of a definite angeioma as in a case attending my out-patients at the present time. Other cases, and this is the most numerous group, are attributed to "heart disease," constipation, pressure by an habitually overloaded colon, and occupation. When necessitating prolonged standing the latter certainly does have an important effect: here the increased pressure is ascribed to the weight of the long column of blood and the effect of gravity in hindering the return of blood from the lower extremities. It must be admitted that in the greater number of cases presenting themselves for treatment no definite cause for the increase in pressure in the veins, and no obvious cause for impeding the circulation can be shown.

The object of the present paper is to suggest a cause for the obstruction to the return of blood, especially in the last group, and to bring forward a method of operative treatment based upon this.

The largest and the most important vein for the return of blood from the superficial tissues of the leg is the internal saphenous which ends above by passing through the saphenous opening to join the femoral, and pursues a vertical and fairly direct course from the inner border of the foot to this point. It is joined by many tributaries, and from its size, length, and great vertical extent any comparatively slight obstruction acting through the long column of blood must have a considerable effect on its more distant branches and radicles. As might be expected, the most common site of varicosity is in the course of this vessel, especially in its lower part, and in its tributaries. It contains a number of valves which are said to vary from seven to twenty-two, but as the result of the dilatation which accompanies varicosity these may become incompetent, so that in advanced cases an impulse on coughing may be transmitted along the column of blood and felt in large varicose veins well below the level of the knee.

I believe that in a considerable proportion of cases of varicose veins, especially in those where the patient follows an occupation requiring prolonged standing, the real cause of the trouble is an obstruction to the flow of blood near its termination where the internal saphenous vein passes through the saphenous opening, leaving the subcutaneous tissues to join the more deeply placed and better supported femoral vein. To understand this it will be necessary briefly to consider the anatomy of the saphenous opening.

This hiatus in the fascial sheath of the thigh is bounded on the outer side by the iliac portion of the fascia lata, which has a sharp, well-defined edge known as the falciform border. The upper portion of this, known as the superior cornu, turns

inwards superficial to the femoral sheath to join Poupart's Ligament. The lower portion, known as the inferior cornu, curves inwards, deep to the termination of the internal saphenous vein but superficial to the femoral sheath, to become continuous with the pubic portion of the fascia lata which covers the pectineus and adductor longus muscles and is attached to the ilio-pectineal line of the pubis. Though there is no sharp alteration in direction, the internal saphenous vein here crosses the well-defined inferior cornu of the falciform edge and joins the femoral vein on a deeper plane, the sharp fascial margin intervening between the two vessels. This arrangement by no means necessarily causes obstruction, but it is a relationship where some additional factor may easily produce a slight but definite degree of obstruction which, acting continuously or intermittently over long periods, may produce far-reaching results. This additional factor is, I suggest, increase in the tension of the fascia lata. In the sitting or recumbent position the fascia lata is relaxed: this can easily be proved by pinching up the muscles of one's thigh while in these positions. In the erect position, on the other hand, the fascia lata is tense: this can be readily verified by attempting to pinch up the thigh muscles while one is standing up. It will be found that though the subcutaneous tissues can be pinched up the muscles cannot, owing to the increased tension of the fascia. If the fascia lata is tense, so also must be the sharp falciform edge with its superior and inferior cornua, the latter between the superficial and deep venous trunks. The obstruction thus produced need not be complete: a slight degree of interference acting over a long time will be quite sufficient to overfill the veins, to cause them to dilate, and eventually to become varicose. A vicious circle will also be started, for the overfull vein will be heavier, and this will tend to cause a dragging which will aggravate and increase the obstruction when the fascia is tense. After a time the weakest valves will become incompetent, and then the effect of the increased pressure will be felt still more in the veins lower down in the leg. The effects of the obstruction need not appear in the upper part of the vein; indeed one would expect the effect of the pressure to extend downwards beyond the obstruction and for its effects to first become manifest in the distant tributaries. True, one does occasionally get the localised swelling known as a saphenous varix. Here the trouble is probably localised to the commencement of the vein by a particularly competent set of valves which protects the distal portion. More generally the valves become incompetent and the back-pressure, increased by the weight of the column of blood, affects first of all the vein and its tributaries below the knee.

There is another cause of obstruction at the termination of the saphenous vein which I also believe to be of importance, and which probably acts together with the increased tension of the fascia lata in the erect position. The internal saphenous is joined close to its termination by several tributaries. These are the superficial epigastric, the superficial circumplex iliac, and the external pudic vein. They may enter the saphenous vein separately or join to form two or even a single trunk. These veins are usually regarded as small and unimportant, but they are often surprisingly large, and the flow from them being from above downwards is in direct opposition to the flow of blood in the internal saphenous. I would suggest that this opposition to the return of blood in the internal saphenous, though probably trivial in the sitting or recumbent positions, may be of considerable importance in the erect position with a tense fascia lata and margin of the saphenous opening.

Though I believe obstruction to the flow of blood from the internal saphenous to the femoral vein brought about in these ways to be an important and frequent cause of varicose veins of the lower extremity, I do not by any means wish to suggest that it is the only cause. Indeed I have no doubt that the others mentioned do exist and are often of importance. It is possible, too, that obstruction to the venous return may sometimes occur in a somewhat similar fashion in the external saphenous vein where it pierces the deep fascia, or even in other situations where there are communications between the deep and the superficial veins.

The Operative Treatment of Varicose Veins

I have for a long time thought that in the operative treatment of varicose veins it is a wrong principle to excise or obliterate the main trunks of venous return, especially the chief of these, the internal saphenous. The blood has to return from the superficial tissues of the leg somehow, and if the main trunk is removed a great strain must of necessity be thrown upon the smaller and less important vessels, with the result that they dilate and become varicose. This will frequently be noticed if patients are examined a year or so after extensive excision of varicose veins, especially when the main trunk of the internal saphenous has been removed. Even though all the affected veins were excised at the original operation, only too frequently fresh veins will be found to be varicose, often actually beneath the operation scars, while in some a large fresh venous channel will be found to have developed in the course of the excised internal saphenous. So impressed was I with the importance of preserving the main veins which drain the subcutaneous

tissues of the limb, that some few years ago I tried transplanting veins which were actually varicose from the subcutaneous tissue to beneath the deep fascia, with the idea that the latter structure would support the dilated and weakened veins in much the same way as an elastic stocking. I have long since abandoned this plan, for a varicose vein is a diseased vein; it is liable to give rise to symptoms whether it is in the subcutaneous tissue or beneath the deep fascia, and it is in such a condition that resolution is impossible. The veins in their new position may become inflamed, thrombosed, and their lumen probably obliterated, while extension of the process is not checked.

It may be taken as a generally accepted fact that if a vein is so seriously affected that operative treatment is required, excision by one of the methods in common use is the only effective way of dealing with it.

While speaking of the obliteration of the internal saphenous it is necessary to mention Trendelenberg's operation, in which the internal saphenous is exposed just below the saphenous opening and an inch or so of the vein, after dividing it between two ligatures, is excised. Trendelenberg's operation was formerly a favourite method of treatment but is now, I believe, much less frequently employed. I have used it a good many times, either as the only method of treatment when I have never seen any benefit, or in combination with excision of the diseased veins when I believe that any benefit has been due to the latter proceeding and not to the ligature and division of the internal saphenous. Trendelenberg's operation is only indicated where there is definite evidence of a long column of blood unsupported by valves extending from the abdomen to the foot. In such cases the advantage to be derived by relief from this extensive back-pressure may outweigh the disadvantages following on the obliteration of the main channel of venous return.

The operative treatment of varicose veins should thus have three objects: (1) to excise those veins or groups of veins which are causing symptoms; (2) to remove the cause of the trouble; and (3) to carry out the above and at the same time to preserve the internal saphenous vein, the main channel for the drainage of the superficial system of veins of the lower extremity.

Excision of the veins alone makes no attempt to deal with the cause, neither, as a rule, is the question of the effect on the circulation taken into consideration.

It is not necessary to say anything about the first of these objects. Any large varicose veins which require removal are first excised, especially any situated below the level of the knee.

In addition to this, in those cases where it is considered that the varicosity is caused by obstruction at the saphenous opening, the plan adopted is to divide the fascia lata from the saphenous opening downwards and to transplant the long saphenous vein beneath the fascia which is then sutured over it: at the same time the tributaries which join the internal saphenous at its termination are divided and ligatured. The indications for selecting this operation will be discussed later: the method of carrying it out is as follows:—

The Operation

The course of the internal saphenous vein is carefully verified. Probably the thickened vein can be felt, but to avoid any uncertainty it should be marked out with carbol fuchsin when the patient is being prepared for the operation. The hip being slightly flexed and everted, an incision about five or six inches in length is made immediately to one side of the vein, preferably the inner, from the saphenous opening to about the middle of the thigh. The vein is then cleared first to the outer and then to the inner side, so that the deep fascia is freely exposed for the whole length of the incision. The vein is thus cleared for the whole length of the wound but still remains attached on its deep aspect to the fascia.

By a little dissection the termination of the vein and the lower and outer margins of the saphenous opening are clearly defined. The superficial circumflex iliac, superficial epigastric, and external pudic veins are then looked for and each is divided between two ligatures. The arrangement of these veins varies and the number to be dealt with varies between one and four. The deep aspect of the saphenous vein is now separated from the deep fascia; a director is slipped under the inferior cornu of the falciform edge and the fascia lata is divided along this to the lower end of the wound. The margins of the incison in the fascia are dissected slightly back and the vein is displaced from the superficial tissues into the bed which is thus prepared for it. The fascia is now sewn over the vein by a continuous suture of fine catgut: this commences above at the saphenous opening and extends to the lower end of the incison in the fascia, care being taken to leave the lower half-inch or so in order to avoid constriction of the vein.

In these manipulations the vein is treated with the utmost gentleness in order to avoid any injury or bruising. It should not be dissected too bare; indeed it is a good thing to see a little of the superficial fat attached to it. It should not be seized by dissecting forceps at all, but may be conveniently manipulated by using an aneurysm needle as a retractor. Care should be

taken to preserve tributaries of any size which may join it. It is particularly desirable to preserve a large branch on the outer side and probably a smaller one on the inner side, each situated a small distance below the saphenous opening. When suturing the fascia over the vein a small lateral slit may be made in the fascial margin in order to avoid any constriction as they join the main trunk. Smaller tributaries may be ligatured and divided. The length of vein which should be embedded beneath the fascia must be estimated in each individual case. As a general rule five or six inches will be sufficient, but in several cases where the whole length of the vein has been dilated and thickened I have continued the incision in a downward direction and embedded the vein beneath the fascia as far as the internal condyle. When the lower half of the internal saphenous in the thigh is tortuous and varicose it should be excised, and the upper half may then be treated in the way described : it is, of course, of great importance under these circumstances to preserve the lateral tributaries. When the whole length of the vein is varicose from the saphenous opening downwards, transplantation beneath the fascia is contra-indicated. I would again emphasise the fact that tortuous varicose veins should not be treated in this way. In such cases, if operation is decided upon, excision of the vein should be carried out, or Trendelenberg's operation may be tried ; but in any case the prognosis as regards recurrence is bad.

Indications for the Operation

Let me say at once that I do not suggest that this operation should be performed indiscriminately. On the contrary, a careful selection of cases must be made. First of all the same well-recognised rules must be followed as in the selection of cases for excision. Cases where the varicosity is general, whether bilateral or unilateral ; where numerous communicating branches between the main external and internal saphenous veins are varicose ; and where the venous radicles are becoming dilated, are not suitable for operative treatment. Chronic swelling of the leg, due to solid œdema, is also a contra-indication, and especial discrimination is required in selecting cases for operative treatment in patients of middle age or over.

Generally speaking, the special indications for transplanting the upper part of the internal saphenous vein beneath the deep fascia are :—

1. The patient must be a young adult, or if of middle age his general health and condition must be satisfactory.

2. The varicosity must affect the lower part of the internal saphenous and its tributaries. Both legs may be affected, but

whether unilateral or bilateral the disease must not be generalised, *i. e.* the small venous radicles must not be involved.

3. Other causes for the condition must be absent, and there must be some evidence to suggest that there is obstruction at the saphenous opening. This is usually indicated by a thickened and dilated condition of the saphenous, which, however, is not tortuous and varicose. The over-distended vein will readily be felt and probably seen when the patient is examined in the erect position, and often in the recumbent position also. This I believe to be an early condition and one in which excision of the varices and removal of the cause offers a good prospect of cure: it is also one which, if allowed to progress, will result in extension of the varicosity until the condition becomes general and unsuitable for operative treatment.

The Results of the Operation

The operation is quickly performed and presents no particular difficulties. In most patients there is no post-operative pain or tenderness along the course of the embedded vein; in a few there is a slight degree of pain, but if the precautions mentioned above are taken, and if the embedded vein is not itself actually varicose, a true thrombosis is certainly very unusual.

I have now performed this operation some twenty times during the past four years. It is perhaps difficult in an individual case, when one sees the patient after an interval of some months, to estimate the degree of benefit attributable to the excision of the diseased veins and the amount that may be ascribed to the operation of the internal saphenous. When, however, one sees a number of cases it is possible to get further light on this point. For instance, I have recently seen the cases of varicose veins upon whom I operated in the hospital last year. Of those written for six turned up for inspection. Three of these were treated by excision of veins and transplantation of the internal saphenous beneath the deep fascia; the other three by excision alone. The three best results were the former group, of whom two might be described as cured and the third, a very extensive case, as greatly improved, for, though there were still a few dilated veins, all symptoms had disappeared. In addition, one other patient who lived some distance from London, and was thus unable to come to the hospital, expressed herself as being free from all symptoms and trouble since the operation.

The results indeed have been so encouraging that I intend to continue this method of treatment and feel justified in bringing it to the notice of others.

OBSERVATIONS ON THE ACIDOSIS * FACTOR IN PREGNANCY AND IN NEPHRITIS

(A PRELIMINARY REPORT)

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THE original object of these investigations was to obtain evidence relating to that hypothesis which assumes a condition of acidosis in cases of pregnancy and of nephritis, a view which has been supported on clinical and therapeutic grounds. The occurrence of albuminuria and œdema in nephritis and in certain forms of abnormal pregnancy suggested a common line of research; but the association must not be understood to imply any supposition of a common pathology.

In attacking a problem of this extent it was necessary to plan a series of observations comprising determinations of the alkali reserve of the blood, acid excretion by the kidneys and lungs, reaction of œdema fluid, and "alkali tolerance." Although we have not yet acquired sufficient material to draw definite conclusions as regards the original thesis, such results have been obtained, particularly by the application of one method, as would appear to justify the publication of a preliminary report.

METHODS

1. *The Bicarbonate Content of the Plasma*

[Before commenting on this procedure, we would emphasise a certain fallacy which might theoretically impair the value of our results in this direction. The bicarbonate content is expressed as molar concentration of $NaHCO_3$ in the plasma. Obviously a true hydræmia would, *per se*, determine a low figure. This factor does not appear generally to have been taken into account by other observers in estimating the plasma constituents, and, indeed, we have good reason to believe that

* The term "Acidosis" is applied comprehensively. In view of the objections to its use recently advanced by the Hæmoglobin Committee of the Medical Research Council,[1] and to avoid ambiguity, it seems necessary to indicate that it here refers to variations in the acid-base equilibrium generally, and not to any particular form of acid intoxication.

it has not influenced our results materially; but it is a point to which we propose giving further attention.]

One object of this paper is to stress the value of the titration method evolved and described by Van Slyke, Stillman, and Cullen.[2] In our experience it is comparatively easy of application once the solutions and apparatus have been prepared; it also appears to give very accurate results, judging from repeated observations on the same individuals on different dates. We have found it quite satisfactory to centrifugalise the oxalated blood under paraffin in the tube in which it is collected. An excess of oxalate should not be used, as laking vitiates the determinations. It is necessary to pay strict attention to the other technical points enumerated in the original account. As we have not hitherto determined the reaction of the blood by the parallel method,[3] we have titrated to the constant end point *p*H 7·4.

Theoretically, it is advisable to obtain readings shortly after withdrawal of the blood, and this we have usually done; but no great depreciation in values appears to result from reasonable delay. The following figures indicate the observed fall in bicarbonate content of plasma due to prolonged delay. In each case the first figure represents an immediate determination, and the second a determination on the same sample of plasma kept at laboratory temperature during the interval indicated.

(1) ·0360 : ·0333 (55 hours).
(2) ·0314 : ·0301 (24 hours).
(3) ·0192 : ·0192 (24 hours).

2. *Acid Excretion by the Kidney.*—We have in general adopted the plan of Henderson and Palmer,[4] who estimate the total acid excretion in 24 hours. This necessitates observation of the following factors:—

Volume;
Hydrogen-ion concentration;
A: the amount of acid in the urine in excess of that combined with the urinary bases as they existed in the blood; this quantity being expressed in c.c. of N/10-solution per diem;
NH_3: the total urinary ammonia expressed in like manner;
TA: $A + NH_3$;
R: $\frac{A}{NH_3}$

The hydrogen-ion concentration has been determined by

the indicator method; the titrable acidity by Cole's modification of Henderson and Palmer's method; and the ammonia by the formol titration method. The latter (ammonia) values therefore include the amino-acid factor, whereas Henderson and Palmer's figures were obtained by Folin's method. In certain cases, Leathe's double titration method [5] has been applied. Rothera's test has been used for acetone and aceto-acetic acid.

THE BICARBONATE CONTENT OF THE PLASMA IN NORMAL MALES AND NON-PREGNANT FEMALES

	No. of observations.	Highest.	Lowest.	Average.
Males . . .	14	·0370	·0311	·0345
Females . . .	8	·0341	·0301	·0319

(These and other bicarbonate values in this paper are expressed as molar concentrations of $NaHCO_3$. Each figure represents an average of three determinations.) The average figure for the male is thus definitely higher than that for the female. Variations have also been noted in the same female, indicating menstrual changes. This latter factor, which we are investigating further, has been detected by other observers from different points of view. Hasselbalch and Gammeltoft [6] have found the alveolar CO_2 tension to fall before menstruation; they have also found a premenstrual rise in the ammonia coefficient of the urine, a fact which has been confirmed by Bond [7] and others.

I. PREGNANCY

It has long been recognised that pregnancy presents conditions of acidosis in various senses of the term. Considerable confusion has apparently arisen in the minds of many authors of obstetric publications on account of the variable terminology; and, in place of a systematic study of the whole problem, we find isolated series of observations made from different standpoints. Hasselbalch and Gammeltoft's [6] researches show the "fixed acidity" of the blood to be increased during pregnancy; the alveolar CO_2 tension is lowered; and the ammonia coefficient of the urine is usually raised. Normally a state of "compensated acidosis" is said to exist. They also suggest a *tendency* to acetonuria, which has been generally recognised. This latter condition, indicating a ketosis, has been demonstrated, in however slight degree, by Harding [8] and Duncan in *all* cases of "morning sickness." It would appear that the two forms of "acidosis" are quite distinct, although the one may be superimposed on and related to the other.

There is reason to believe that a depletion of glycogen from the maternal liver is responsible for the "morning sickness" and its accompanying ketosis. Possibly the vomiting itself provides an accessory form of compensatory acid excretion. More severe forms of vomiting occurring in the earlier periods of pregnancy represent a state of extreme starvation and dehydration such as can explain all the observed phenomena. It is sufficient for the present merely to refer to the importance of the psychological element which undoubtedly plays so large a part in the accentuation of this complication of pregnancy.[9]

Returning to the more general aspect of acid-base equilibrium, we are not as yet in a position to account for the variations, nor can we explain the acidosis which appears to characterise eclampsia. It seemed possible that calcium depletion might play a certain part in disturbing the balance; but, as will be seen, the observations made in that direction have on the whole proved negative. Even those variations in the calcium content of the serum detected by other observers may be accounted for as *secondary* to the acidosis.

Estimation of Calcium in the Serum.—These determinations have been made by one of us (F. C.) after the method of Laidlaw and Payne.[10] As this method has only recently been devised, it may be of some service to attempt to assess its practical value. With certain reservations, it appears to be extremely accurate, even in the hands of an unskilled chemist. In nearly every case two samples of each serum under investigation were treated separately from the earliest stage (ashing), and yet almost invariably the results agreed to within ·002 mg. per c.c. The chief objection to the method from a clinical point of view is the time involved: to estimate the calcium in two sera (with duplicate controls) occupies at least an hour and a half per day on three successive days. Although the process can be completed on the second day if required, the actual time spent cannot well be curtailed. Secondly, the absolute value of the determination depends entirely on the accurate composition of the alizarin solution. Considerable difficulty has been experienced in obtaining a reliable standard. For this reason it has been necessary to reject a number of observations in the present series. Of some thirty determinations (with duplicate controls) only nineteen have been accepted. In these the accuracy of the alizarin standard has been verified experimentally by checking against a solution of known calcium content.

Total calcium content of serum, expressed in milligrams per c.c.:—

Non-pregnant women :

·098
·094
·096

Normal pregnancy :

·093 (third month)
·093 (eighth month)
·093, ·095, ·092, ·094 (ninth month)
·098, ·094

Pregnancy with albuminuria :

·093, ·098, ·098, ·094 (ninth month)

Eclampsia :

·098 (ninth month)
·094 (full term)
·098 (eighth month)

Nephritis (non-pregnant woman) :

·089

It will be seen that these figures show little if any variation from the normal. De Wesselow [11] has found a very slight fall in serum calcium during the later stages of uncomplicated pregnancy, most marked in the sixth and seventh months; but he regards the average values as remaining within physiological limits. Kehrer,[12] estimating the calcium of whole blood, found a definite diminution during the later months; but this method is undesirable, unless hæmatocrit determinations are also carried out, as the element is unevenly distributed between plasma and corpuscles. The association of albuminuria with pregnancy also appears from the above figures to have practically no influence on the calcium values of the serum. The eclampsia figures are noteworthy, although only three in number, since other observers have found a very low calcium content in this condition. Further investigation is needed. De Wesselow,[13] in an excellent review of the biochemistry of the blood with relation to its calcium and phosphate content, gives references to the original observations. Halverson,

Mohler, and Bergeim,[14] who incidentally note a decrease in eclampsia, record interesting observations on the calcium factors in pernicious vomiting of pregnancy and in uræmia. In the former, although the serum calcium remains normal, the excretion of calcium, as might be expected, is increased, together with that of ammonia and acid; but in uræmia and certain cases of nephritis the serum calcium values are low, whilst the excretion of calcium is definitely decreased. They correlate these latter findings with an increase in serum phosphate.

As is well known, the blood normally contains calcium salts in approximately saturated solution, and therefore the administration of calcium by mouth has little or no effect in raising the concentration. On the other hand, Haldane [15] has recently shown that the ingestion of calcium *chloride* may lead to a definite acidosis. This, of course, does not apply to the organic salts.

Up to the present, we have not investigated the calcium content of the blood in relation to menstruation. It is also to be noted that only the *total* calcium (in ashed serum) has been estimated. Possibly an application of Vines' [16] biological method may demonstrate a relative deficiency in ionic calcium, particularly in view of the variations in acid-base equilibrium with which we are dealing. Nevertheless, such data as we have obtained do not lend encouragement to the view, advanced by certain well-known authors, that calcium metabolism is the dominating feature in the economy of the female.

Bicarbonate content of plasma.—Standard concentrations have already been noted. Although it appears that the average bicarbonate content of the plasma in females is lower than that in males, it may here be repeated that the average figure found in non-pregnant women was ·0319.

The following values have been obtained in *Uncomplicated Pregnancy :—*

·0282 (third month)
·0270 (fourth month)
·0275 (fifth month)
·0245
·0282
·0272 (ninth month)
·0257
·0261

Average : ·0268

In Pregnancy with Albuminuria:

·0287 (seventh month)
·0273
·0257
·0277 (ninth month)
·0275

Average: ·0274

In Eclampsia:

·0210 (ninth month)
·0209 (full term)
·0180 (eighth month)

Average: ·0200

In Early Pregnancy with Chronic Nephritis:

·0215

These data demonstrate a lowering of the bicarbonate content of the plasma in pregnancy. The variations from month to month have yet to be determined; but the fall appears to occur at an early stage of pregnancy, and a correspondence is observed between this lowering of the alkali reserve and that of the alveolar CO_2 tension traced by Hasselbalch.[6]

Contrary to our expectations, simple "albuminuria of pregnancy" is *not* accompanied by any further diminution. The eclampsia figures are significant, however, and tend to support Hasselbalch's view that this condition may present a real or "uncompensated" acidosis. Unfortunately only three cases have been available since the commencement of this research.

Acid Excretion in the Urine.—The following determinations are compared with Henderson and Palmer's [4] average (normal) values. I. and II. represent typical cases of uncomplicated pregnancy; III. represents a case of albuminuria of pregnancy with œdema. All had reached full term. I. and II. had been admitted to hospital for Cæsarean section on account of small pelvis, without other observed abnormality.

	I.	II.	III.	H. and P.
Plasma bicarbonate .	·0282	·0272	·0273	—
	Urine (24 hours).			
Volume . . .	1750	840	1000	1231
Sp. g. . . .	1016	1025	1022	—
*p*H . . .	6·4	5·8	5·4	5·94
A	262	320	270	278
NH_3 . . .	573	510	540	370
TA	835	830	810	649
$R\left(\frac{A}{NH_3}\right)$ . . .	·46	·62	·5	·75

No casts, sugar, acetone, etc. Albumen in III. only.

It is to be repeated that the " ammonia " in our cases was estimated by the formol-titration method, and therefore includes the amino-acid factor, which may entirely explain the higher figures, although Hasselbalch and others have demonstrated an increased ammonia excretion during pregnancy. The " total acidity " values and the ratios given are subject to the same criticism. It is, however, reasonable to include the amino-acids, as in acid urine they serve the same purpose as ammonia in neutralising acid.

The only point which we would advance at the present time is that the total acid excretion in the urine certainly does not seem to be decreased. As the corresponding plasma bicarbonate values are low, and as the alveolar CO_2 tension has been shown to be decreased, we may possibly assume an increased acid production in pregnancy. We wish to emphasise, however, that we have no intention of regarding this " compensated acidosis " of pregnancy as a pathological condition.

For obvious reasons it is difficult to obtain reliable twenty-four-hour specimens of urine from female patients, and our observations in the majority of instances have necessarily been incomplete. In only one of the cases of eclampsia was it possible to obtain a small specimen of urine before treatment commenced — *p*H 5·6; albumen ++; no acetone or aceto-acetic acid. As treatment in each case included the application of bicarbonate, etc., further observations were of little scientific value. In the same case, *p*H readings on successive days during recovery were 5·8, 6·4, and 6·6. Unfortunately, little significance can be attached to determinations of the *intensity* of urinary acidity as indicating total acid excretion under these pathological conditions, particularly in view of the oliguria which commonly characterises eclampsia. However, in a case of nephritis complicating early pregnancy, in which the plasma bicarbonate figure was ·0215 (practically the same as that in the eclampsia cases) the *p*H reading of the urine averaged 7·4 over several days, pending the induction of abortion. In this case the blood area figure was three times its normal value.

Such facts as we have hitherto been able to adduce tend to support the view that normal pregnancy is associated with an increased production of acid, and that eclampsia is accompanied by a still greater *accumulation* of acid, but this latter may be partly or wholly due to retention on the part of the kidney.

Clifford White [17] has conducted a clinical research on the lines of Sellards' [18] " alkali tolerance " method. Although this method is open to serious objections as a scientific procedure, the results obtained were certainly impressive.

Assuming the acidosis for the moment, we have yet to explain its nature, and its association with the other observed facts of pregnancy "toxæmias." It is tempting to apply the theory recently advanced by McCarrison,[19] which suggests that the action of adrenalin is enhanced in conditions of acidosis, and that its output may be actually increased. The comparatively rapid rise in blood pressure which accompanies the onset of many cases of eclampsia is a feature which demands attention. It is even possible that the glycogen depletion observed by Harding [8] may be due to suprarenal glycogenolysis thus originated. However, there is no definite reason to suppose that adrenalin in particular is the determining factor. Any of the pressor bases may produce the same effect, which indeed may be due to entirely different causes.

II. Nephritis

Considerable difficulty has been experienced in obtaining a sufficient number of cases under suitable conditions for investigation; but the figures already obtained appear to be significant and worth recording. In this section also it is intended to include some clinical observations on nephritis in relation to the "acid" factor in this disease.

During the course of an inquiry into the prognosis, immediate and remote, of a large series of cases of nephritis in children undertaken by one of us (A. A. O.) it became apparent that three factors of importance operated to retard recovery, or, in chronic cases, to produce exacerbations. In order of importance these factors are:—

(1) Infection or re-infection;
(2) Over-exertion;
(3) Inadequate diet.

The second of these, over-exertion, has a direct bearing upon the problems discussed in this paper. It has always been recognised that complete rest in bed for a lengthy period is extremely important in the treatment of nephritis, and this procedure is based on sound principles. It is well known that athletes are found to have albumen and even casts in the urine after severe exercise. Increased acid output by the kidneys after muscular exertion has also been demonstrated by numerous observers. It seems probable, therefore, that in nephritis a relatively slight degree of exertion will operate adversely where the kidney is already damaged in two of its chief functions, viz. to assist in the regulation of the acid-base balance of the body, and to maintain the protein content of the blood.

In uræmia a condition of acidosis has been definitely established, but in nephritis without uræmia the evidence is less complete and less conclusive. As outlined above, the problem can be attacked in three ways: by observations upon (1) the alveolar CO_2, (2) the acid-base balance of the blood, and (3) the acid excretion by the kidney; and these three factors must be taken together into consideration before conclusions can be drawn as to the existence of an acidosis.

In presenting the following figures of the bicarbonate values of the plasma in nephritis it must therefore be noted that they are in no sense given here as conclusive evidence of acidosis. The cases from which these values were obtained were not under standard conditions as regards exercise and diet, and several of them were unfortunately having alkalies by mouth when examined; but as far as possible these factors have been indicated in the table.

No.	Type of Case.	$NaHCO_3$.	Œdema.	Alkalies.	Remarks.
1	Uræmia	0·0120	Nil	Nil	Up. Full diet. Restricted meat.
2	Parenchymatous nephritis	0·0113	Extreme	Nil	Out-Patients.
3	Acute nephritis	0·0130	Slight-face	Nil	Bed. Milk. Farinaceous.
4	Pregnancy and nephritis	0·0153	Nil	Nil	Bed. Light full.
5	Subacute nephritis	0·0268	Face and legs	Pot. Cit. gr. 60 per diem.	Bed. Milk. Farinaceous.
6	Uræmia	0·0279	Nil	Pot. Cit. gr. 90 per diem.	Up. Light full. Restricted meat.
7	Parenchymatous nephritis	0·0157	Slight	Pot. Cit. gr. 60 per diem.	Milk. Light full. Salt free. Bed.
8	Subacute nephritis	0·0273	Face and feet	Pot. Cit. gr. 70 per diem.	Bed. Milk. Salt free.
9	Mixed nephritis. Uræmia	0·0160	Extreme	Nil	Bed. Light full. Salt free.
10	Pregnancy and nephritis	0·0215	Nil	Nil	Bed. Light full.

It will be seen that the readings are low as compared with the normals given above, and some are extremely low. Furthermore, those cases which were having moderate doses of alkalies at the time of the determinations gave, as might have been expected, higher readings, with the exception of No. 7.

It may be objected that in many cases of nephritis there is a watery state of the blood or hydræmia, and that the low figures obtained are but an expression of the degree of plasma dilution. In the cases marked with a star in the table the samples of blood withdrawn were so low in corpuscular content as to suggest the possibility of a general dilution; but in the other cases this was not observed. It is probable that in certain types of nephritis with anasarca and hydræmia a low reading may be the result of plasma dilution, and this point is now under investigation; but it cannot be the explanation in all cases,

especially in the interstitial variety. In diabetes mellitus with ketosis a low plasma bicarbonate is also found, and there is here no associated hydræmia. In chlorosis, where the blood volume has been shown to be increased, the bicarbonate value is normal.

In studying the acid output by the kidney in nephritis, two methods of procedure can be adopted. A few cases can be observed under strictly controlled conditions with regard to diet, exercise, etc., involving accurate determinations upon intake, excretion and total metabolism; or a large series of cases can be studied under average conditions and the results treated statistically. Up to the present we have been unable to obtain sufficient figures by either of these methods to form any definite conclusions; but we have been impressed with the *variability* in urinary reaction and acid output by the kidney in cases of nephritis. Henderson and Palmer [20] have published an important series of observations bearing on this point.

Considering that acid excretion is one of the chief functions of the kidney, it is a matter for some surprise that so little attention is given to it in the treatment of nephritis and that it is often disregarded entirely. Small doses of alkalies are frequently prescribed presumably for their alleged diuretic action; and mild alkaline drinks advocated chiefly for the purpose of "flushing out the kidneys." These measures, though entirely inadequate, indicate that the value of alkali therapy is dimly realised though probably wrongly interpreted. In most cases of nephritis careful daily estimations of the albumen output are made, though the significance of this abnormality is not properly understood. Albuminuria has, in fact, dominated the picture in Bright's disease to such an extent that diet and habits of life are prescribed largely with a view to reducing this symptom to a minimum, more important considerations being neglected.

The following two cases are reported in some detail to illustrate certain apparent effects of the administration of sufficient alkali to bring the blood bicarbonate up to a normal level. The first case was treated empirically before the bicarbonate titration method had been adopted.

Case 1.—Gladys W., æt. 19, admitted under Dr. G. H. Hunt in August 1921 for œdema of the face, legs, thighs and ascites. She was a typical example of chronic parenchymatous nephritis, and after three months in bed on a light, salt-free diet, the œdema disappeared and she returned home, passing less than 1 part per 1000 albumen. At home she remained on a farinaceous and salt-free diet, but after a few days the œdema

returned. In February 1922 she was readmitted very œdematous and anæmic, and passing from 6 to 7 parts of albumen per 1000. The blood urea was normal. With rest in bed and on the same low diet most of the œdema again subsided, but she continued to pass the same amount of albumen per day. It was then noticed that after large enough doses of Pot. Cit. and Sod. Bicarb. to render the urine alkaline to litmus, the daily output of albumen was roughly halved, the other conditions being the same. The reaction of the urine was tested by litmus paper only, but the figures are noteworthy—

Date.	Reaction.	Average daily albumen. Parts per 1000.	Drugs.	Diet, etc.
12.12.21 to 19.12.21	Acid	6	nil	Strict bed. Farinaceous. Salt free.
20.12.21 to 30.12.21	Alkaline	3¼	Potus Imperialis ad lib.	,,
17. 2.22 to 22. 2.22	Acid	6½	nil	,,
23. 2.22 to 9. 3.22	Alkaline	1¾	Pot. Cit. gr. 180 per diem.	Light full with salt.
10. 3.22 to 11. 3.22	Acid	7	Acid Sod. phos. gr. 60 per diem.	,,
13. 3.22 to 23. 3.22	Alkaline	3¾	Pot. Cit. gr. 180 per diem.	,,
24. 3.22 to 7. 4.22	Acid	11	nil	Light full with salt. Limited meat. Extra vegetables and sugar.
8. 4.22 to 5. 5.22	Alkaline	7	Pot. Cit. gr. 180 per diem. Soda Bicarb. gr. 100 per diem.	,,

She returned home in July 1922 with only a slight degree of œdema and passing about 7 parts of albumen per 1000. Her subsequent history is interesting. She has been leading a perfectly normal life at home on full diet with salt, and makes a habit of walking two or three miles a day for exercise. Throughout this period she has been taking sodium bicarbonate gr. 100 and potassium citrate gr. 120 per diem, doses which have been found sufficient to keep the urine just alkaline to litmus. On one occasion she was supplied by mistake with half the requisite amount of alkali, and shortly afterwards there was a slight return of œdema in her legs. Since then she has been perfectly free from symptoms, though all the time she has been passing from 7 to 10 parts of albumen per 1000. This case is still under observation and bicarbonate values of the plasma are being taken at intervals (a recent determination gave the figure ·0301).

Case 2.— Emily H., æt. 29, admitted under Dr. A. P. Beddard in January 1923 for œdema of face and neck. A month before admission the face and eyelids became swollen, following the extraction of some teeth. Removal of more teeth was followed

in ten days by further swelling in the same situations as before, hæmaturia, and albumen and casts in the urine. She was confined to bed, placed on a light full diet after the hæmaturia had been controlled and was not given alkalies. A hæmolytic streptococcus was grown from the teeth. The œdema of the neck subsided, but the face and eyelids remained swollen. On 17.1.23 the urine was acid to litmus, and a twenty-four-hours specimen showed, *p*H = 6, A = 126·5, NH_3 = 276, TA = 402·5, R = 0·458. Albumen a trace. Volume 1150. Sp. g. 1015. Plasma bicarbonate = 0·0193. Sodium bicarbonate ʒii and Pot. Cit. ʒii were given daily for one week, when further observations were made. On 28.1.23 urine alkaline to litmus. Twenty-four-hours specimen: Vol. 1300; *p*H 7·6 +; A nil; NH_3 234; Sp. g. 1018; albumen nil; plasma bicarbonate 0·0305. During this week the œdema of the face and eyelids considerably decreased; by the end of the week it was only noticeable in the early mornings.

In nephritis it can always be argued that recovery takes place at any time spontaneously, and that long remissions are frequent; but we are not attempting here to prove that alkali therapy is a cure for nephritis, or indeed for any condition in which a low plasma bicarbonate exists. It seems reasonable to suppose, however, that where a low bicarbonate value is found some good may result from restoring the level; and we believe the clinical improvement, which coincided in these cases with adequate administration of alkalis, to support this contention.

"Alkali Tolerance"

Palmer and Van Slyke [21] and Palmer, Salvesen and Jackson,[22] have shown that the alkali retention test originally suggested by Sellards [18] may be not only misleading but even dangerous in disease, especially nephritis. Under pathological conditions, an unusually high concentration of bicarbonate in the blood may be required to turn the urine alkaline; moreover, variability in absorption from the gastro-intestinal tract may affect the accuracy of the result. Nausea, vomiting and diarrhœa have followed excessive bicarbonate administration, whilst in certain cases the level of blood bicarbonate attained has been well within the range where tetany is known to occur.

It is therefore essential to control adequate alkali administration by determinations of the plasma bicarbonate. The above authors have suggested a formula for the approximate restoration of the normal level, based on a preliminary estimation of the plasma CO_2. We have modified this formula to

facilitate the calculation where values are obtained and expressed in terms of plasma bicarbonate :—

$$g = 58{\cdot}8 \times B \times w.$$

g : weight in grammes of sodium bicarbonate to be administered;
B : desired increase in molar concentration of bicarbonate;
w : body weight in kilogrammes.

We wish to express our indebtedness to those members of the Staff and others who have allowed us to make observations on their cases, and also to those who have afforded us advice on many points, particularly to Dr. J. H. Ryffel and Mr. W. W. Payne. Dr. Ryffel has not only willingly advised us throughout, but he has also given us every facility for work in his laboratory.

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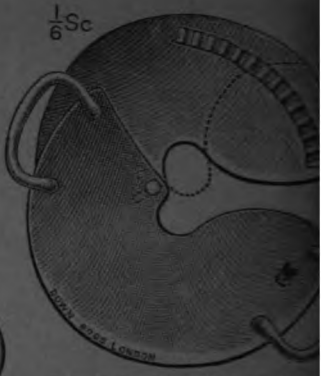

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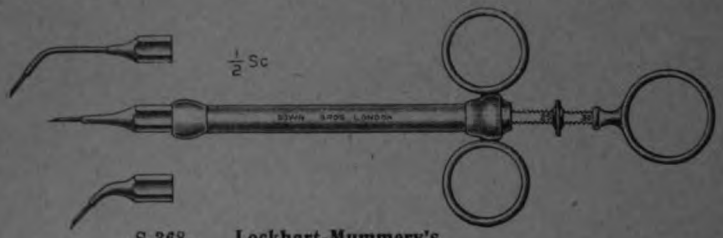

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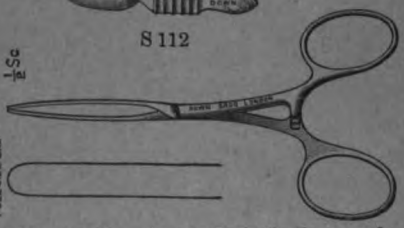

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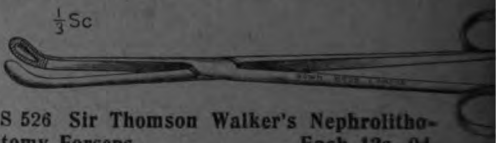

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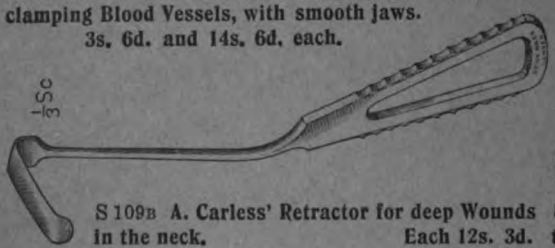

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CHLOROSIS

A STUDY OF THE GUY'S HOSPITAL CASES DURING THE LAST THIRTY YEARS, WITH SOME REMARKS ON ITS ETIOLOGY AND THE CAUSES OF ITS DIMINISHED FREQUENCY

By J. M. H. CAMPBELL, M.D., Senior Demonstrator of Physiology and Hilda and Ronald Poulton Fellow, Guy's Hospital.

THERE is a widespread belief that chlorosis is much less prevalent to-day than it was twenty or thirty years ago. Sometimes this is attributed to improved conditions of housing, feeding and living; sometimes the cause is left unexplained, and sometimes part of the reduction is supposed to depend on the improved methods of diagnosis. It seemed worth while examining the figures of various hospitals to find out if the decline was general, and during what years it took place, to note whether these changes could be definitely related with any other changes, medical, social or economic, and to see if they threw any light on the etiology of chlorosis and particularly on the cause of its lower incidence.

This paper is written mainly from the one point of view; but incidentally, while the case reports and literature were under review, some other aspects have been touched upon. To the symptoms, treatment and prognosis there is nothing new to add. As many cases as possible were collected where the gastric contents and function had been examined, because the recent evidence that achlorhydria is practically always present in Addison's anæmia adds interest to the findings in other types of anæmia. Particular attention was paid to the colour-index and to the relative changes in chlorosis and other types of anæmia, and these are fully discussed. Finally, some experimental investigations on the volume of the blood and changes in its specific gravity have been reviewed to see what light they might throw on the etiology of chlorosis.

PART I. INCIDENCE OF CHLOROSIS AT VARIOUS ENGLISH HOSPITALS (1888–1922)

The yearly incidence of chlorosis as judged by the number of cases admitted to Guy's Hospital can be studied for thirty-

five years (1888–1922). Unfortunately before that year statistics could only be obtained with great difficulty, as no system of indexing of diseases was in use. Chlorosis and other anæmias are separately indexed throughout this period. The number of cases admitted during each year is shown in Chart I. It shows clearly (1) a sharp rise and fall between 1888 and 1892 with a maximum in 1890; (2) a period of slight fluctuations with a tendency to rise, reaching a maximum in 1908 at a point considerably below the peak of 1890; (3) a sharp fall from 1908 to 1910; and (4) a period of fluctuations with a tendency to fall—the whole at a lower level than any previously reached since 1888. There are two possible criticisms of these figures—that the numbers dealt with are too small to give any reliable index of the changes, and that the exact meaning of chlorosis may have varied from time to time under the influence of different teachers. Both these objections are met to some extent by taking the figures from other widely separated hospitals over the same period of years, and the second point is considered in some detail later. For those readers who do not like figures a perusal of the case records of chlorosis admitted to Guy's Hospital during the three periods 1890, 1908 and 1920–1922 will show, perhaps even more clearly than graphs and tables of figures, that the type of the disease has changed little and that it has enormously diminished in incidence. Short case reports for these three periods are given in the Appendix. The year 1890 was chosen because of the large number of cases. Forty-three were indexed as chlorosis, and thirty of these are included, as the case reports were full enough to be certain of the diagnosis. In twenty-one of these there was a record of a characteristic blood picture. I do not think the year 1890 was unusual; in the following year, of the thirty-five cases diagnosed chlorosis, eighteen were proved by blood counts and very complete records. After 1906 the reports of all cases diagnosed as chlorosis have been examined, and the proportion of " proved cases " to total cases is much the same as in 1890 (see Table I).

Originally the figures for three London hospitals only were analysed, but later many more statistics were put at my disposal, and I wish to thank Professor A. J. Hall for the great help he has given me in this and other matters, and also the authorities of the various hospitals who have allowed me to make use of their figures. Generally the statistics are only available from 1898 onwards, but at the Sheffield Royal Hospital Out-patients figures are available for almost the same period as for the Guy's Hospital In-patients. The results

are given as the percentage of cases of chlorosis to total medical Out-patients in each year, and they are shown graphically in Chart I. There is not a close detailed agreement with the Guy's curve, but there is a striking general agreement. From 1891 to 1905 (instead of 1892 to 1908) there are fluctuations with a gradual rise; from 1905 to 1907 (instead of 1908 to 1910) there is a sharp drop; and from that time on there are only slight fluctuations at a much lower level than any time previously.

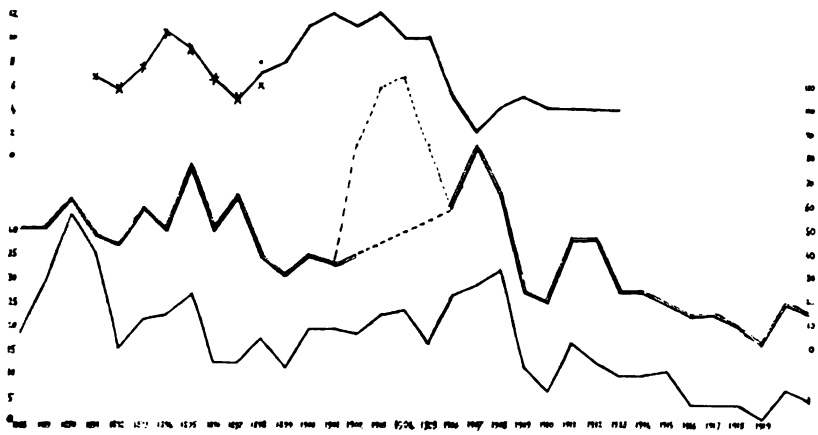

CHART I.

INCIDENCE OF CHLOROSIS.

The bottom line shows the number of cases of chlorosis treated as In-patients at Guy's Hospital against the lower left-hand scale.

The middle line shows the total number of cases indexed as chlorosis or anæmia, other than pernicious (Addisonian) or splenic anæmia, against the right-hand scale. (The years 1902–1906 are joined by two dotted lines because the registrar indexed cases of anæmia rather differently during those four years.)

The top line shows the proportion of cases of chlorosis to total medical Out-patients at the Sheffield Royal Hospital (1891–1898, Professor Hall's Out-patients; 1898–1914, all Out-patients), against the upper left-hand scale.

The data on which this paper is based were obtained from the statistics of the Out-patients of the Birmingham General Hospital and the Sheffield Royal Hospital, and the In-patients of the Royal Infirmary, Sheffield, of the Royal Infirmary, Glasgow, and of Guy's, St. Thomas's,[1] St. Bartholomew's[2] and the London hospitals.

Hospital statistics of the years of the war are not very reliable for comparative purposes, as some beds were closed and often figures were not published as fully as at other times, but there were available figures for sixteen years (1898–1913). In Table I the figures for these various hospitals are given for the twenty years 1898–1917, and it is quite clear that the

enormous decrease during the war years only intensifies a decrease which was already taking place. The American figures given by Cabot [3] are also added for comparison, and the figures for three year periods are added below to eliminate minor variations.

In the reports of St. Thomas's and St. Bartholomew's Hospitals before 1907 the figures for anæmia are given without further detail, but after 1907 the various anæmias are separately classified. By taking the proportion of chlorosis to all anæmias for the years 1907–1912, an estimate can be obtained of the number of cases of chlorosis during the earlier years. As far as this method is inaccurate it will err by minimising any decline in the incidence of chlorosis.

The figures for the separate hospitals show great variations from year to year, but there is general agreement in a rise during the earlier part of the period under review, often culminating in a maximum in 1903, followed by a decline sometimes rather gradual and sometimes rather irregular. At Birmingham there was a large increase from 1898 to 1903, with a subsequent steady fall only interrupted by a smaller rise about 1908. The Glasgow figures also reached a maximum in 1903 and the subsequent fall was continuous. In Sheffield it is interesting to compare the figures of the In-patients of the Royal Infirmary and the Out-patients of the Royal Hospital (see Charts I and II). At one there is a high level from 1898–1904, with peaks in 1898 and 1902; in the other a high level from 1898–1905, with the maximum from 1900–1903. In both cases this is followed by a sudden drop in consecutive years and the figures remain steady at a low level. Taking these three widely separated centres, the figures for the three years 1910–1912 are less than half those for the three years 1901–1903, and the figures for the years 1913–1916 are in each case still lower; the figures for the year 1913 are actually less than one-sixth of those for the year 1903.

At the four London hospitals the results are less striking. At Guy's, apart from the years at the end of the last century, the highest figures were for the years 1906–1908, with a smaller peak in the years 1903–1904. At the London Hospital the highest year was 1910 and the second highest 1903. At St. Bartholomew's there was a general regular fall from 1899, and at St. Thomas's the figures were more constant than elsewhere, with rises in 1905 and 1909.

The period of the decline is more variable than the period of increase from 1899–1903. At Sheffield the fall was greatest from 1904–1907, at Glasgow from 1905–1909, and at Birmingham

it was only slight till 1912–1918, when it became very great. In London also it was later, at Guy's especially from 1908–1910, at St. Thomas's from 1909–1913, at St. Bartholomew's from 1908–1912, and at the London, although it started from

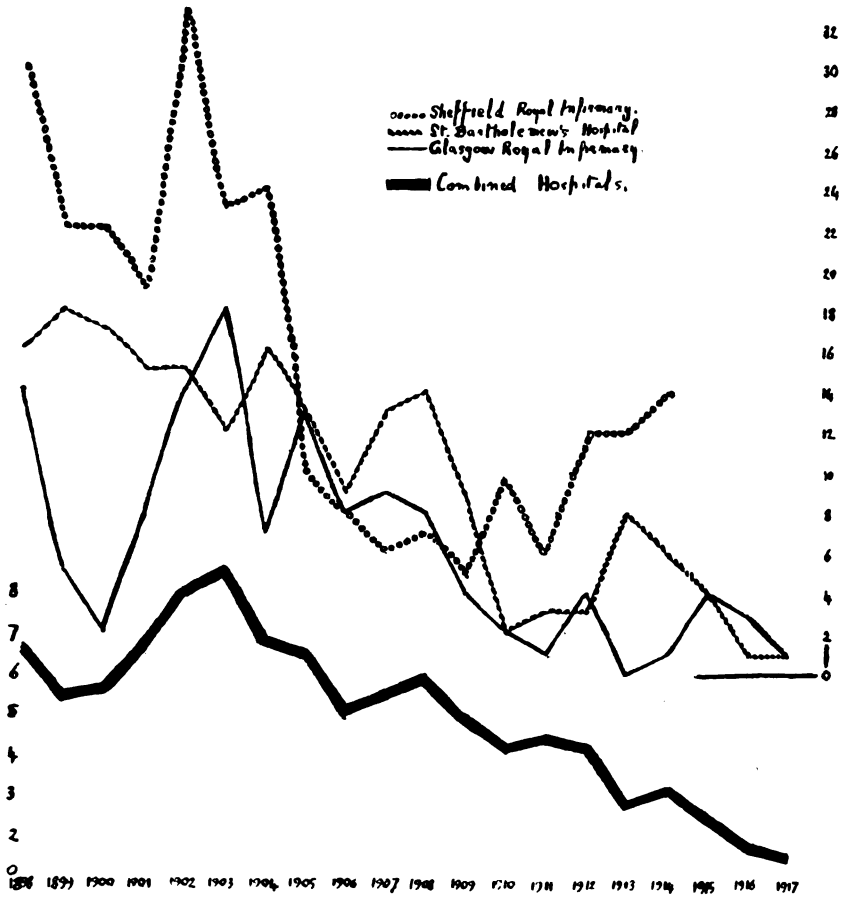

CHART II.

INCIDENCE OF CHLOROSIS.

The upper curves show the number of In-patients with chlorosis in three general hospitals against the right-hand scale.

The lower thick curve gives the incidence of chlorosis in Great Britain from the combined figures of all the hospitals given in Table I.

1910, it was not as marked as elsewhere until the first full year of the war, 1915.

In every case the years of the war (1915–1917) are the lowest of any three consecutive years except at Glasgow, where the years 1911–1913 are even lower. Extraneous factors may account for this slightly, but the fall is so great that there must

be some fundamental reason, and it is only an exaggeration of a fall which was already taking place. Where the figures are available for the years of the war (1915–1917) they are one-quarter, one-third, one-fifth, one-seventh, and one-fortieth of the figures for the years 1901–1903. Taking them all together there were five times as many cases of chlorosis during the early years of this series as during the years of the war.

After the war only figures for Guy's Hospital have been obtained. There is some evidence of an increase, but it is very slight compared to the previous decrease. The years up to 1917 are given in Table I, and for subsequent years they have been 1918, 3 (1 "proved"); 1919, 0; 1920, 6 (4 "proved"); 1921, 4 (2 "proved"); and 1922, 3. These latter cases are described in the Appendix and show little change from those of 1890; *e. g.* Case 128 was unusually severe and of the old type, and made a rapid and uneventful recovery with iron.

The figures for Guy's Hospital and the Sheffield Royal Hospital are shown in Chart I. The curves for the shorter period for the Sheffield Royal Infirmary, the Glasgow Royal Infirmary and St. Bartholomew's Hospital are given in Chart II. The results for the eight hospitals are combined in a single curve which gives a good idea of the general trend after eliminating local variations. There is a rise from 1899 to 1903 and a steady fall from 1903 to 1917. The curve is obtained by taking the figures from each hospital as of equal importance and expressing the cases of chlorosis in any one year as a percentage of the cases during the twenty years in that hospital.

The complete figures, on which these conclusions are based, are given in Table I.

This decrease in the incidence of chlorosis has been generally recognised for many years, but the only other well-known figures are those of Cabot for the Massachusetts General Hospital for the years 1898–1907.[3] The main drop was in the years 1900–1902, which is just before the beginning of the drop in England. On the whole it seems to have started earlier in the large provincial towns than in London. Cabot's figures also showed that the drop was not due to increasing treatment of the same girls as Out-patients, for it was equally marked and occurred a little earlier. This is shown by the In- and Out-patient figures of the two Sheffield hospitals, and physicians working at Out-patients are in general agreement that the disease is rarer there, as it is in the wards. Dr. Achard has written to Professor Hall that in his opinion and that of his colleagues the diminution is equally apparent in France.

TABLE I.

CASES OF CHLOROSIS (1898–1917).

Year.	In-patients.						Out-patients.				
	Guy's Hospital, London.	St. Thomas's Hospital, London (1).	St. Bartholomew's Hospital, London (2).	The London Hospital, London.	Royal Infirmary, Glasgow.	Royal Infirmary, Sheffield.	Royal Hospital, Sheffield. Percentage of total medical Out-patients.	General Hospital, Birmingham.	Massachusetts General Hospital, America (Cabot) (3).	Total British figures. Percentage.	Guy's Hospital: cases with blood counts with percentage of haemoglobin less than 60.
1898	17	(5)	(16)	10	14	30	8	40	23	6·6	—
1899	11	(5)	(18)	12	5	22	8	40	35	5·4	—
1900	19	(6)	(17)	10	2	22	11	35	25	5·6	—
1901	19	(8)	(15)	9	8	19	12	95	14	6·7	—
1902	18	(4)	(15)	11	14	33	11	175	3	8·0	—
1903	22	(5)	(12)	16	18	23	12	180	4	8·5	—
1904	23	(6)	(16)	12	7	24	10	115	4	6·8	—
1905	16	(10)	(13)	8	13	10	10	90	1	6·5	—
1906	26	(3)	9	14	8	8	5	110	2	5·1	9
1907	28	3	13	14	9	6	2	150	—	5·5	13
1908	31	4	14	10	8	7	4	180	—	5·9	15
1909	11	11	9	4	4	5	5	175	—	4·9	6
1910	6	5	2	23	2	11	4	130	—	4·2	4
1911	16	7	3	16	1	6	4	145	—	4·4	7
1912	17	3	3	14	4	12	4	125	—	4·2	4
1913	9	0	8	13	0	12	4	30	—	2·8	4
1914	9	4	6	12	1	14	—	15	—	3·1	4
1915	10	—	4	5	4	—	—	5	—	2·5	3
1916	3	—	1	4	3	—	—	—	—	1·8	1
1917	3	—	1	2	1	—	—	—	—	1·5	3
Total	314	89	195	219	126	264	—	1825	—	100·0	—
1898–1900	47	(16)	(51)	32	21	74	27	115	83	17·6	—
1901–1903	59	(17)	(42)	36	40	75	35	450	21	23·2	—
1904–1906	65	(19)	(38)	34	27	42	25	315	7	18·4	—
1907–1909	70	18	36	28	21	18	11	505	—	16·3	34
1910–1912	39	15	8	53	7	29	12	400	—	12·8	15
1913–1915	28	(8)	18	30	5	(38)	—	50	—	8·4	11

( ) denotes uncertain figures; see text.

Changes in the Use of the Word "Chlorosis" during the Last Century

Before taking these figures as proving a real diminution in chlorosis, one must know if the word has been used in exactly the same sense during the period under review. At an earlier date, as judged by Ashwell's paper,[4] the meaning was not quite the same, though it is easy to recognise from his very

clear description of the signs and symptoms the cases which would now be diagnosed as chlorosis.

Ashwell defined chlorosis as "a peculiar affection of the general health, most frequently seen at the time when puberty is or ought to be established, invariably connected with absence of menstruation or with irregularity and imperfection of this function." Later he described it as "a feeble, morbidly undeveloped condition of the system, existing probably from infancy, but assuming at puberty a marked and peculiar form." He states that it was of very frequent occurrence.

From his paper it is obvious that he recognised the sex and age incidence, the disturbance of menstruation, the breathlessness and œdema of the feet, the constipation and changes in the appetite, and the ready cure which could be effected with iron and treatment of the bowels. He differs from the modern view in dividing his cases into two groups—the simple cases of chlorosis and the cases complicated with organic change in the lungs, which appear from his description to be cases of tuberculosis of the lungs.

He realised the much greater danger of this latter type and discusses the relation at length. "The question is not unimportant, whether the phthisis be induced by the chlorosis and amenorrhœa, or whether these latter affections do not owe their origin to the phthisical tendency of the system. Occasionally phthisical lesions of the lung may be induced by chlorosis, but in far the greater number of instances the chlorosis seldom does more than excite into activity the previously latent tendency to this fatal disease."

He also recognised the tendency to hæmatemesis—a point which will be alluded to again. "A vicarious discharge of blood from the stomach by vomiting is not an unusual concomitant of protracted chlorosis and amenorrhœa. In such cases the treatment may have been partially successful and . . . the suspension of the catamenia continuing, congestion or engorgement occurs in some of the organs of digestion and nutrition; a quantity of dark venous-coloured blood is thrown up."

Ashwell's paper is still of great interest because of his full and careful descriptions. Apart from his belief in vicarious menstruation, and in the benefits following the establishment of menstruation even after disease of the lungs was established, there is little which is not still in accordance with the medical views of to-day.

May I quote finally from his views on treatment? "It is not my intention to amplify this paper by an elaborate

comment upon certain great and fundamental mistakes in the physical management of female youth. And yet I must be excused if I direct attention to the diet, air, exercise and clothing of the sex. It will readily be granted that if in these particulars there is extensive deviation from the dictates of nature and common sense, there must be a proportionate risk of debility and disease. If the national prejudices in these particulars could be changed, chlorosis would be uncommon instead of being, as it is now, an extremely prevalent disease. . . . It is superfluous perhaps to observe that warm clothing, regular exercise by walking or on horseback are valuable auxiliaries; and as soon as the repugnance to them can be conquered, nutritious animal diet and mild malt liquor will be productive of benefit. At this crisis some of the preparations of iron may be exhibited, and the sulphate is probably the most efficacious. Occasionally the effect of iron is almost magical, especially where it does not confine the bowels, nor induce febrile heat. I do not dwell on the value of travelling because it is universally admitted that nothing contributes more to health and cheerfulness than change of air, of scene and of temperature." And a little further on he adds, " Three or four leeches have been applied to the mammæ on alternate days with very doubtful effect as to the restoration of the menstrual function," and " Marriage frequently cures chlorosis; yet its good effects are not certain and invariable. A passing allusion is all that is necessary on its remedial influence; as in the chlorosis of early life, such a connection is unlikely and distant; and even at later periods its existence is not a matter for medical discussion and control."

So much for the views of the early part of the last century on chlorosis. It is unfortunate that there are no statistics to show what its prevalence then was, but from this paper and from the cases which are quoted it was certainly very common.

From 1888 to the present day at Guy's Hospital there have been certain changes in the usage of the word. About 1890 it was used very much as at present; this is most clearly shown by a perusal of the cases in the Appendix. In these no close relationship to phthisis is noticeable. Since Ashwell's time the incidence of phthisis had enormously diminished, so that it would be expected much less as a complication of chlorosis. It has sometimes been suggested that some cases of apparent chlorosis were really slight cases of phthisis without sufficient changes in the lungs to give physical signs. But there are many points in the etiology of chlorosis, notably its age and sex incidence and its favourable course, which do not fit in

with this view. Moreover, severe anæmia is not common as an early sign of phthisis, though it frequently occurs later.

In the Guy's Hospital reports for the years 1906–1908, and probably elsewhere, case sheets were frequently indexed as Hæmatemesis, Chlorosis. On reading the reports some were similar to the cases of gastrostaxis described by Hale White,[5] and others had the usual symptoms of gastric ulcer, and were treated as such by the physician in charge. They would now more usually be indexed as Gastric Ulcer and Secondary Anæmia, and so are not included as chlorosis. Nor are the gastrostaxis cases included, because it is impossible to know how far the anæmia was due to the loss of blood. In any case all patients with hæmatemesis have been excluded because they fall into a different category.

Hale White's views about gastrostaxis have not been universally accepted, but the facts on which he based his conclusions cannot be denied. Although gastric ulcer in surgical and post-mortem statistics is more common in men, and occurs later in life, hæmatemesis is more common in young women, and in many of them the general symptoms and appearance of the stomach are unlike those of gastric ulcer. Whether young women are particularly liable to acute gastric ulcers and hæmatemesis, or whether there is a true condition of gastrostaxis may remain undecided. It is not of importance from the present point of view, but it is of importance that these conditions occur especially in young women, because of the supposed association between chlorosis and gastric ulcer.

Be that as it may, there is obviously a difference in the use of the word chlorosis during this period, and to elucidate this the 83 cases diagnosed chlorosis during 1906–1908 were specially examined. Nearly half were cases of chlorosis with a percentage of hæmoglobin 60 or less, and including a few cases where there was no blood count, at least 60 per cent. were typical cases of chlorosis, and would be included as such by any definition of the term. Rather more than a fifth were cases with definite hæmatemesis, and rather less than a fifth were other cases which may have been chlorosis or may have been secondary anæmia of some obscure sort.

The exact results are shown in Table I. In the first column are all cases diagnosed as chlorosis. In the last column only cases with a hæmoglobin percentage under 60, and in other ways typical of chlorosis, are included. The two sets of figures generally run parallel, though about 1906 there is rather wider divergence than at other times. If allowance is made for this difference it would explain a small part of the drop in the

years before the war. Between 1890 and the present day there is very little difference in the use of the terms, and blood counts seem to have been done quite as frequently then as now.

One can conclude that there may have been at times slight differences in the meaning of chlorosis, but these changes in the diagnosis are not great and can only account for a very small part of the diminution in the incidence of the disease. The decline has been continuous but irregular throughout the period under review. It is more particularly the severe cases which have disappeared, though such do still occur, as, for example, a girl who was recently under Dr. Fawcett with a hæmoglobin percentage of 25 and retinal hæmorrhages, who made a rapid and lasting recovery with Blaud's pills (Case 128).

Incidence of Chlorosis in Sweden

Since writing the above, Dr. Hurst has drawn my attention to a very interesting paper by Schauman [11] on the falling incidence of chlorosis in Sweden and Finland. He records a paper by Huss to a medical congress at Stockholm in 1851, stating that chlorosis had become a common disease in Sweden during the preceding twenty years, having been unknown previously. Obviously from Ashwell's paper [4] it was common in England when it was rare in Sweden, and Huss was quite aware of its earlier description and did not in any way regard it as a new disease. From his time until 1870 its course was followed in Norway by Lund, where it remained more or less steady with irregular increases. Schauman's paper is based on three sets of statistics : those of Warfvinge for the Stockholm Hospital for 1879–1903; of Köster for the Gottenburg Hospital for 1890–1919, and of Willebrand and himself for the Helsingfors Hospital for 1897–1920. The figures are very similar to those for the various English hospitals in showing general agreement, with slight variations in the exact years at which changes began.

Warfvinge's analysis of 683 cases at Stockholm showed a large and steady rise from 1887–1892, and an equally steady fall from 1892–1897.

Köster's figures for Gottenburg showed a sudden large increase from 1892–1893, a very sudden drop from 1901–1902, marked variations from 1902–1912, with no high figures, and after 1912 a steady drop to practically no cases after 1916.

Schauman and Willebrand's figures for Helsingfors show a big drop from 1898–1899, followed by a more gradual decline to 1912, since when cases have been very rare.

It seems equally true in Sweden and Finland that chlorosis

diminished rapidly and suddenly some time between 1892 and 1902, since when it diminished more slowly, and almost disappeared about 1912 or 1916. Schauman states that there is the same experience in general, as in hospital practice, and quotes Pallitzer for similar conclusions in Vienna.

Conclusion

There is good evidence that chlorosis has diminished enormously in England, the United States of America and Sweden during the last thirty years, and verbal evidence of the same change in France and in Vienna. Probably, therefore, the change is almost world-wide, though it may not be universal.

In different parts of Sweden it seems to have taken place between 1893–1902, in America about 1900–1902, and on the whole rather later in England, though at Guy's, which provides the only statistics for the end of the last century, there was also a big fall in 1891. In Sweden, where the figures go back further, there is some evidence of an earlier increase suggesting a possible periodicity in the incidence of chlorosis, but this is much less certain than the decrease.

A more difficult question remains. What is the cause of the comparative disappearance of chlorosis? This can be discussed better after certain other aspects of chlorosis have been considered.

Part II. Changes in the Blood

As these are the changes which are best recognised and have been most fully investigated, it is best to deal with these first. Changes in the colour-index, in the blood volume and in the specific gravity of the blood will be discussed.

Colour-index

It is frequently stated that the colour-index in chlorosis is lower than in secondary anæmias, but this is not borne out by the Guy's figures. In Chart III the colour-index is plotted against the hæmoglobin percentage in a hundred consecutive blood counts in chlorosis. Obviously as the hæmoglobin percentage falls the colour-index becomes lower and lower, and if a line is drawn representing the mathematical mean of all the colour-indices for each decade, it shows that the drop is regular, being 0·8 for 80 per cent., 0·6 for 50 per cent., and 0·4 for 20 per cent. hæmoglobin. This drop corresponds with the diminishing size of the average red cell as the anæmia becomes more severe.[12]

A similar chart has been drawn for a hundred consecutive blood counts in cases of secondary anæmia, mostly cases of

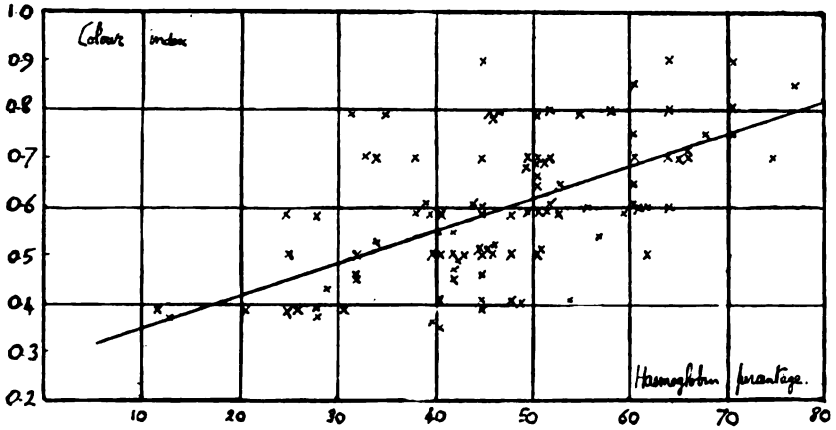

CHART III.

Colour-index and hæmoglobin percentage in 100 cases of chlorosis. X indicates single blood examinations and the straight line shows the general relationship.

hæmatemesis and menorrhagia, where the anæmia is produced by the loss of relatively large amounts of blood. It is shown

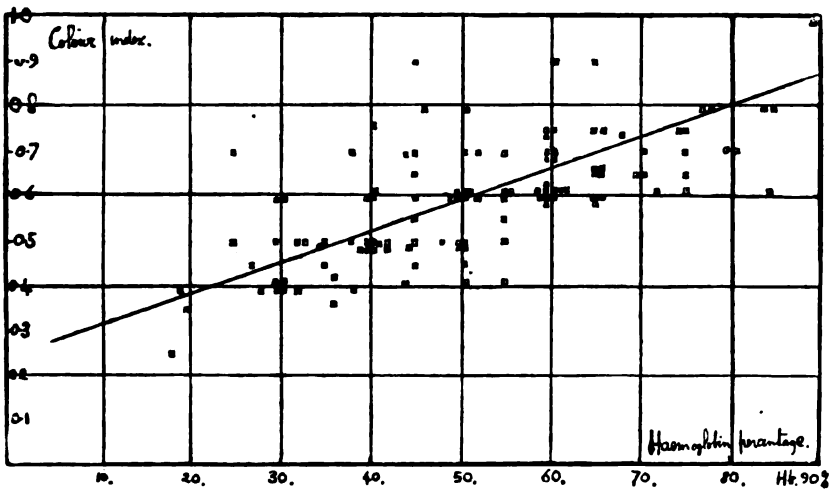

CHART IV.

Colour-index and hæmoglobin percentage in 100 cases of secondary anæmia. ⊡ indicates individual cases, and the straight line shows the general relationship.

in Chart IV. The range of variation is very similar, and the line representing the mathematical mean is almost exactly the same as in cases of chlorosis. Capps [13] showed that the average

colour-index in his large series of cases of chlorosis was the same as the colour-index in a large series of cases of rapidly produced secondary anæmias though the colour-index was rather higher in the secondary anæmias which were produced more gradually over a long period of time. His cases were all combined in one group average, but the similarity is much more striking where averages are taken for each decade and are found to be the same. Such a close resemblance is strong evidence that the same pathological process is at work in

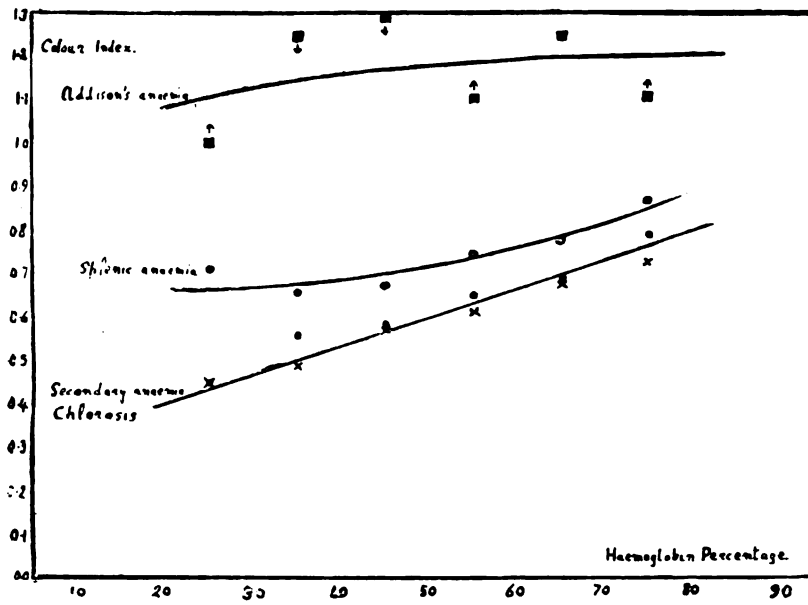

CHART V.

Colour-index and hæmoglobin percentage in chlorosis, secondary anæmia, Addison's anæmia and splenic anæmia. (See Table II.)

chlorosis and in secondary anæmia, though there are many difficulties in accepting this view. They are discussed later.

Similar charts have been made from over two hundred blood counts in Addison's anæmia taken from the paper by Campbell and Conybeare,[14] and from eighty-three blood counts in splenic anæmia taken from Osman's papers [15] and other cases in the Guy's Hospital Reports. The line representing the mathematical average for each of these four groups is shown in Chart V. The lines for chlorosis and secondary anæmia are practically the same and the colour-index falls with the hæmoglobin percentage. In Addison's anæmia the colour-index remains above one, however low the hæmoglobin falls. Splenic

anæmia occupies an intermediate position, the colour-index falling from 0·8 with 70 per cent. to 0·6 with 20 per cent. hæmoglobin. This is a further interesting difference between splenic and other anæmias. There is so much difference between Addison's anæmia and chlorosis that very few individual determinations of the two groups overlap in spite of the wide range of variation. The colour-index is of very little help in the diagnosis of splenic anæmia, because individual counts overlap the lower part of the area for Addison's anæmia and practically all the area for chlorosis. The figures from which these lines are drawn are given in Table II. The number of cases is given in brackets, and the figures are obtained by taking all the counts where the hæmoglobin is between 40 and 30 per cent. and taking the average colour-index; *e. g.* for chlorosis there are eighteen counts where the hæmoglobin is between 30 and 40; in these the colour-index varies between 0·36 and 0·6 (one case 0·7), the average being 0·49.

The changes in the colour-index in chlorosis and secondary anæmia are exactly the same, and it has been shown [12] that the changes in the size of the red cells in these two conditions are also the same.

TABLE II.

AVERAGE COLOUR-INDEX IN VARIOUS ANÆMIAS.

Hæmoglobin percentage.	Colour-index in			
	Chlorosis.	Secondary anæmias.	Splenic anæmia.	Addison's anæmia.
Under 30	·45 (11) *	·45 (11)	·72 (10)	1·0 (58)
30–40	·49 (18)	·56 (15)	·66 (9)	1·25 (46)
40–50	·58 (25)	·58 (31)	·67 (14)	1·3 (49)
50–60	·61 (28)	·65 (22)	·75 (16)	1·1 (21)
60–70	·68 (20)	·69 (16)	·78 (15)	1·25 (17)
Over 70	·73 (16)	·8 (5)	·87 (17)	1·1 (16)

* The figures in brackets give the number of cases.

Blood Volume

Since the original discovery of Haldane [18] and Lorrain Smith [19] that the blood volume was enormously increased in chlorosis, great interest has centred round this change, although it has not been universally accepted. Their conclusions, based on a very large number of cases, were that the normal blood volume was about 3·2 litres, and that in severe cases of chlorosis this might be increased even to double the normal figure, though this was unusual. In seven slight cases of chlorosis

with an average hæmoglobin percentage of 68 the blood volume was normal; in twenty-one of average severity the blood volume was 4·9 litres, and in two with a hæmoglobin percentage of 23 the blood volume was 6 litres. When the weight of these patients was allowed for the relative increase in the blood volume was somewhat greater. It is sometimes forgotten that changes in the blood volume were found in other anæmic states. In six cases of secondary anæmia following hæmorrhage (Hb. percentage 33) the blood volume was 3·9 litres. In anæmia following infection with ankylostomum it was 4·0 litres, and in seven cases of pernicious anæmia, with an average hæmoglobin percentage of 26, it was 4·5 litres. The blood volume in pernicious anæmia was very variable, but in the other conditions the change was constant. An even larger blood volume was found in cases of polycythæmia and congenital heart disease, the average being 6·5 litres.

The increased blood volume is not a peculiarity of chlorosis, but occurs sometimes in pernicious anæmia, and constantly in all other anæmias, though the increase is considerably greater in chlorosis. The validity of the carbon monoxide method has often been called in question, but Douglas showed that it gave good agreement with the direct Welcker method,[25] and more recently this has been confirmed by Plesch [26] and by Whipple and his fellow-workers.[27] Plesch also found an increased blood volume in chlorosis and secondary anæmia, but, as would be expected, he found it decreased in several cases shortly after a large hæmorrhage. He found that the blood volume was also increased in certain cases of heart disease, arteriosclerosis and chronic nephritis.

An increased blood volume may occur in so many conditions that it does not appear likely to throw much light on the etiology of chlorosis, but there was one important difference between chlorosis and the other anæmias. The total oxygen capacity, which is the same as the total amount of hæmoglobin, was diminished in chlorosis, but when the weight of the patients was taken into account, the relative oxygen capacity was not diminished except in the most severe cases, where it was reduced to about three-quarters. In the other anæmias the oxygen capacity relative to the weight was reduced to half the normal. It is very difficult to see why the blood volume should be increased in anæmia. As would be expected in anæmia following hæmorrhage, the total amount of hæmoglobin was reduced to half; but because the blood volume was increased, the average hæmoglobin percentage was only a third. This further dilution of the blood would appear to be a dis-

advantage, and no adequate explanation has been found. Probably this is one reason why many people have been unwilling to accept the views of Haldane and Lorrain Smith.

In chlorosis it is even more difficult, because there appears to be a normal amount of hæmoglobin in the body, and the anæmia is produced by a dilution of the blood with normal plasma. But from the point of view of most of the cells of the body there is a true anæmia—it matters not how it is produced—and this is shown by the production by the bone marrow of the small cells which are its characteristic response to loss of blood. The low colour-index is produced in this way.

Against this mass of evidence must be set the work of Bock [28] and others with methods depending on the injection of some easily recognised substance which is diluted in the plasma. Bock found in all the conditions he investigated that the volume of the plasma was constant and that changes in the total blood volume simply depended on changes in the volume of the corpuscles. If this was true the blood volume would be diminished in chlorosis and in secondary anæmia.

Whipple [27] has suggested an explanation of these experiments which appear to be contradictory. He points out that the direct Welcker and the carbon monoxide methods only measure the hæmoglobin or the volume of the corpuscles, and that the injection methods only measure the plasma. Both groups of methods assume that the total blood volume can be calculated from either of these factors and from the proportion of corpuscles and plasma found in venous blood by the hæmatocrit. If the blood corpuscles are not uniformly distributed in different parts of the body this assumption would not be justified, and it would explain why the different methods gave different results for the total blood volume. He brings forward a certain amount of evidence which is not very conclusive in support of this view that the blood corpuscles are not equally distributed throughout the body. It has been known for a long time that different parts of the capillary circulation may contain very different amounts of corpuscles and plasma, and the recent work of Krogh [29] on the nervous control of the capillaries and on the changes in their calibre and corpuscle content has amplified this knowledge. Another possibility is that corpuscles may be held in some of the larger vessels of the internal viscera; for example, in the sinusoids of the spleen. It is difficult to accept this as the whole explanation of the big differences found by Haldane and Lorrain Smith in chlorosis. Probably it accounts for part of the change in chlorosis where the volume is found to be so greatly increased by the CO method.

Another fact which may be of importance is the experimental observation of Cohnstein and Zuntz [37], that section of the cord in dogs increases the blood volume considerably. If this change follows section of the cord, it may take place to a lesser extent under nervous stimulation of other sorts, and a loss of tone of the blood vessels, including the veins and capillaries, might cause a considerable increase in the blood volume. This seems a very likely factor in chlorosis.

There are still technical difficulties in the various methods for determining blood volume, and because of these the following conclusions can only be tentative. But if the results of the different methods are accepted, and there is a large amount of evidence collected by many workers, it follows that in all anæmias and some other conditions there are considerable changes in the blood volume and in the distribution of corpuscles throughout the body which intensify the apparent degree of anæmia. Little is known about such changes, but Krogh's recent work has shown their possibility. In chlorosis the anæmia would be largely produced by such changes in the distribution of the blood and the capacity of the circulatory system, and this explanation would remove chlorosis from the primary blood diseases. The other blood changes which have been discussed would also group chlorosis with the secondary anæmias, and later, further reasons will be adduced for not looking on the changes in the blood as the essential feature of chlorosis.

These observations have not at present made the problem any more easy to solve. The change in the size of the red cells and in the colour-index means that there is a real change in blood production, and this is intensified by the dilution of the blood or its unequal distribution. Apart from the injection of hypertonic fluids or other substances which raise the osmotic pressure, little is known about factors which may cause an increase of blood volume. But something is known about the production of anæmia by lack of nutrition or by toxins inhibiting the bone marrow, apart from anæmias produced by excessive loss or destruction of blood corpuscles. Brown and Roth [20] have described and investigated such cases of anæmia in association with nephritis. Such a cause may be an additional factor in the production of chlorosis, and no doubt a diet deficient in iron acts in this way.

A final point of interest, though its significance is not clear, is that Mahnert [30] and others have found that the blood volume is increased during the latter part of pregnancy.

The Specific Gravity of the Blood

Many years ago Lloyd Jones [17] showed that the specific gravity of the blood was low in chlorosis. He also found it low in most other anæmias. At first sight this seems a confirmation of the views of Haldane and Lorrain Smith, but he showed that the plasma was not diluted, but had a normal specific gravity, and that the change was simply due to the deficiency of red corpuscles. This seems to make his observations lose any special significance they might have for the understanding of chlorosis, but his investigations on the changes of the specific gravity of the blood of normal men and women are of such great interest in understanding chlorosis that they seem worth recording rather fully, especially as they are not widely known.

He examined the specific gravity of the blood in fourteen hundred men and women, and the range of variation is shown in Chart VI. In boys the specific gravity varied between 1044 and 1054, and gradually rose till at the age of 30 it was between 1054 and 1064. In girls the upper limit is very similar, starting at 1056, crossing the line for boys at 12 or 14 and rising gradually to the same point. The lower limit is strikingly different. Till 14 the lower limit is slightly above the line for boys. From 14 to 16 there is a sudden sharp drop from 1050 to 1041, at which point it remains until 22. From 22 to 28 it rises rather rapidly, and after 28 more slowly, getting gradually nearer to the lower limit for men, which it reaches about 50. After 50 the limits of variation for men and women are very similar and both fall slightly. The important point is that from 16 to 22 the specific gravity of the blood may be much lower in women than in men, and that from 22 until the menopause it is somewhat lower.

Lloyd Jones examined the specific gravity of the blood in one hundred and twenty young women with chlorosis. Exactly during the years when the drop occurred in the apparently normal girls there was a much greater drop in the cases of chlorosis. In not a single case of chlorosis was the specific gravity up to the mean value for women, and the mean value in chlorosis was very nearly the same as the lowest limits found in the apparently healthy. These observations were all made in whole blood, and Lloyd Jones himself and others found that the specific gravity of the plasma was unchanged. The importance of these facts is, that they prove the tendency to chlorosis in the apparently healthy girl at the period of puberty. Of the eight hundred women examined from whom the curves

in Chart V have been drawn, nearly 10 per cent. fell into the low area which would have been excluded as abnormal in men.

A further point is brought out in the lowest curve in the

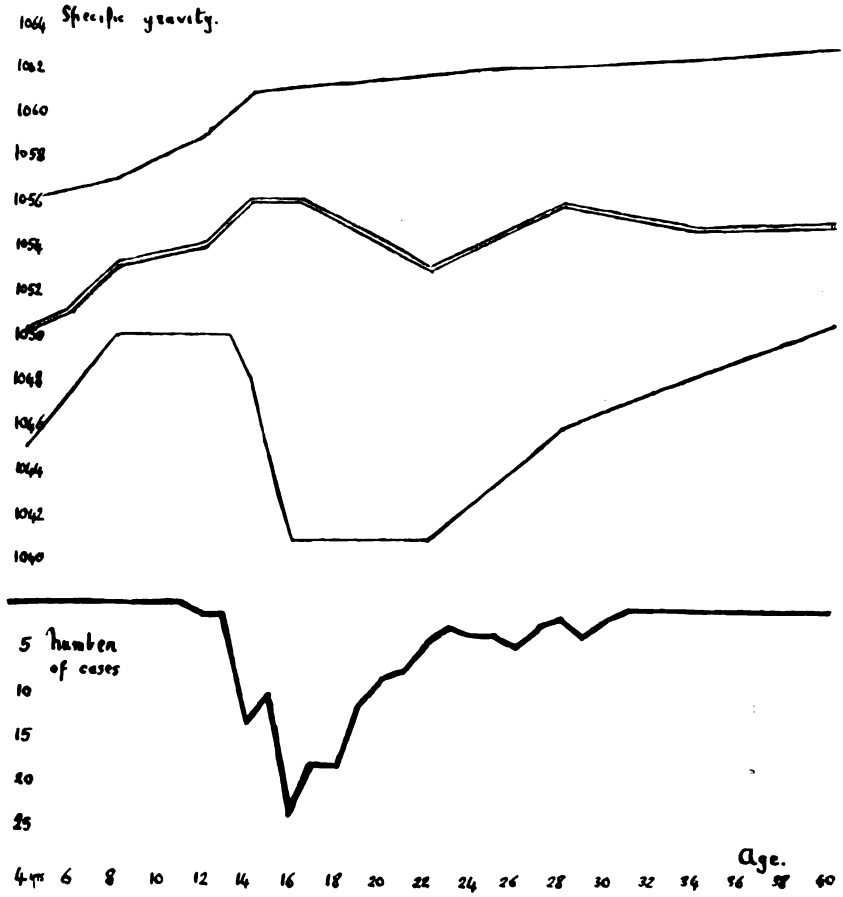

CHART VI.

SPECIFIC GRAVITY OF THE BLOOD IN NORMAL WOMEN, AND AGE INCIDENCE OF CHLOROSIS.

The three upper curves show the mean specific gravity of the blood of women at various ages with the limits of variation (Lloyd Jones).

The mean specific gravity in 120 cases of chlorosis was almost exactly the same as the lowest limit compatible found in health.

The lowest thick line shows the age incidence of chlorosis, inverted to show that it closely agrees with the period when the specific gravity of the blood may fall.

chart which shows the age incidence of the cases of chlorosis in this series. It corresponds closely with the drop in the curve of the specific gravity of the blood. This latter drop is prolonged further than the age incidence curve, but the disease

lasts for some time and relapses, so that the two curves could not be expected to coincide more closely.

A tendency of anæmia at this age has been directly noticed by others, but not so definitely and not on such a large scale. The frequency of the low specific gravity of the blood in apparently healthy women at the age of puberty, and the similarity of the two curves for the age of this change and for the age incidence of chlorosis, suggest strongly that chlorosis is an exaggeration of a physiological change occurring in all girls rather than a disease *sui generis*.

Part III. Symptoms, Treatment and Prognosis

General Symptoms

There is nothing new to add under these headings, but while the case reports were under review it seemed worth comparing the results with Cabot's conclusions on his series of five hundred cases. Obviously these figures are minimal ones, as a symptom may have been present without any note being made. Breathlessness was the most constant symptom complained of, and this was mentioned in over 90 per cent. as compared with 80 per cent. in Cabot's series. Weakness, lassitude and undue fatigue were referred to almost as frequently, but were not included in the statistical table. Œdema of the feet was noted in over 40 per cent. (60 per cent. Cabot). Fainting attacks were of frequent occurrence—at least 30 per cent.; this is of special interest, because during 1921–1922, of a hundred and fifty patients who attended the Neurological Department for fits, mostly epileptic, at least three were suffering from fainting attacks of an unusually long and severe nature, and were readily cured with iron pills. Unfortunately no special notes were made about headaches. Cabot states that they were present in 85 per cent. of his series, but they were less common in this series. So much for the general symptoms.

Gastro-intestinal Symptoms and changes in Gastric Secretion

The symptoms referred to the gastro-intestinal tract are of special interest because of the possible relationship to gastric ulcer and because of the gastro-intestinal symptoms in Addison's anæmia. Cabot gives dyspepsia as the most constant symptom, occurring in practically every case, nausea and vomiting as less common (60 per cent.), and constipation as present in at least 80 per cent. These figures are practically the same for the incidence of constipation; symptoms of indigestion are only mentioned

in about 60 per cent. of these cases, and sometimes there was a note of good appetite, regular digestion and regular opening of the bowels. No notes were made of the frequency of vomiting, but it was less common than in Cabot's series. Dr. Hurst has suggested to me that just as one or other symptom may be absent in any particular case, sometimes the anæmia may be absent. It has been supposed that constipation and gastro-intestinal disorders are the cause of chlorosis; but their absence in many cases, the frequent occurrence of these symptoms without anæmia, and the sex and age incidence disprove this. It is therefore generally assumed that the anæmia is the cause of the other symptoms, but it may well be that both are the result of some common cause. It is clear that the diarrhœa of Addison's anæmia and the constipation of chlorosis cannot both be caused by anæmia, and it is probable that the former depends on the achlorhydria. Similarly it may be that the constipation and some other symptoms depend directly on the unknown cause, and if this be so, they might occur sometimes without the anæmia. Dyspepsia is very common at all ages, but often it occurs in young women with some of the symptoms of chlorosis without much anæmia, and sometimes these cases respond well to treatment with iron. Beddard has given an admirable description of these cases under the title of "anæmic vomiting," [31] and thinks that a wrong diagnosis of such cases may partially explain the much greater frequency of the diagnosis of gastric ulcer in young women than in young men. He does not give much detail of the blood condition in these patients, but the article suggests that in many of the cases the anæmia need not be very severe.

Most of the other symptoms are common to any anæmia and occur in about the same number of cases in chlorosis, Addison's anæmia or secondary anæmia; *e. g.* breathlessness, weakness, palpitation, fainting and œdema of the feet.

With the gastro-intestinal symptoms it seems best to discuss the changes which take place in the gastric secretion. Von Noorden [33] has collected together the observations on this subject up to 1908. Of thirteen independent observers, six found a marked tendency to hyper-acidity, and only one found a tendency to sub-acidity. In secondary anæmia he states that the results are much more variable, but that there is a general tendency to sub-acidity.

In Table III are collected examinations of the gastric contents in various anæmias in patients who have been in Guy's Hospital recently. Nearly all are observations by the fractional method. The arbitrary method of classification

TABLE III

RESULT OF FRACTIONAL TEST-MEAL EXAMINATIONS IN VARIOUS CASES OF ANÆMIA

Age.		Disease.	Hæmoglobin percentage.	Colour-index.	Test-meal.
		Males.			
1.	26	Hæmophilia; hæmatemesis; secondary anæmia.	43* (25–56)	—	Hyperchlorhydria.
2.	54	Pyelo-nephritis; secondary anæmia.	34-40	1·0	Hyperchlorhydria.
3.	65	Rectal polyp; anæmia.	44	1·3	High normal.
4.	42	Splenic anæmia.	52	0·5	Achlorhydria.
5.	58	Oral sepsis; anæmia.	48	0·65	Normal.
6.	50	Jaundice; ? carcinoma of the liver; anæmia.	38	0·6	Normal.
7.	42	Gastric ulcer; hæmatemesis.	65	0·6	Low normal.
8.	54	Gastric ulcer; hæmatemesis.	40	0·75	High normal.
9.	52	Myxœdema and anæmia.	56	1·1	Normal.
10.	30	Splenic anæmia.	36	0·55	Hypochlorhydria.
		Females.			
11.	35	Splenic anæmia.	50	—	Achlorhydria.
12.	38	Spleno-medullary leukæmia.	30–50	0·6	High normal.
13.	44	Fibroid of uterus; anæmia.	28	0·5	Low normal.
14.	28	Uterine sepsis; anæmia.	59	—	Achlorhydria.
15.	36	Hæmorrhoids; anæmia.	30	0·4	Normal.
16.	36	Gastric ulcer; anæmia.	42	0·5	Hyperchlorhydria.
17.	50	Gallstones and anæmia.†	42	0·9	Achlorhydria.
18.	45	Gallstones and anæmia.	40	0·4	Achlorhydria.
19.	54	Gastric ulcer; anæmia.	20–45	0·4-0·7	Hypochlorhydria.
20.	39	Menorrhagia; anæmia.	50	0·8	Achlorhydria.
21.	37	Secondary anæmia.	55	0·8	Hypochlorhydria.
22.	27	Gastric ulcer; hæmatemesis.	56	0·8	High normal.
23.	27	Menorrhagia.	68	0·7	High normal.
24.	22	Anæmia; ? phthisis.	68	—	Achlorhydria.
25.	48	Oral sepsis; anæmia.	50	0·55	Achlorhydria.
26.	45	Hæmatemesis; anæmia.	36	0·4	Hypochlorhydria.
27.	40	Menorrhagia; anæmia.	60	0·7	Low normal.
28.	22	Anæmia and vomiting.	64	0·7	Low normal.
29.	38	Oral sepsis; anæmia.	54	1·0	Achlorhydria.
30.	39	Menorrhagia and oral sepsis.	35	0·5	Normal.
		Chlorosis.			
31.	21	Chlorosis.	48	0·5	High normal.
32.	21	Chlorosis.	25	0·65	Normal.
33.	18	Chlorosis.	46	0·5	Low normal.
34.	16	Chlorosis.	60	0·6	Hyperchlorhydria.
35.	18	Chlorosis.	60	0·9	Hyperchlorhydria.
36.	23	Chlorosis.	54	0·55	High normal.
37.	22	Chlorosis.	30	0·6	Low normal.

* At time of test-meal. Several blood counts during the previous six months showed that the hæmoglobin had varied from 25 to 56.

† Post-mortem; not pernicious anæmia.

suggested by Bell [34] in a discussion of the findings in various medical conditions has been used, because it is easy to apply and gives comparable results. Like other observers he found achlorhydria in all the six cases of Addison's anæmia examined, and in the five cases of secondary anæmia he found achlorhydria in two and normal curves in three cases. The men and women are separately tabulated because he found that in various medical conditions achlorhydria, hypo-chlorhydria and low normal curves were more common in women, while hyperchlorhydria and high normal curves were more common in men.

In splenic anæmia there were two cases of achlorhydria and one of extreme hypochlorhydria. Cases of Addison's anæmia have not been included in the table because in the long series investigated there are only two possible cases where this disease was not associated with achlorhydria. The constancy of achlorhydria in Addison's anæmia and its relative frequency in splenic anæmia might suggest that any long-continued anæmia might result in achlorhydria. D. Hunter [35] rather inclines to this view and quotes a case of severe anæmia following duodenal ulcer, where hypochlorhydria was present and persisted long after the anæmia was cured. This is interesting because of the almost constant findings of hyperchlorhydria in duodenal ulcer. Against it may be set especially Cases 1, 2 and 12 in Table III. All three were under observation several months in hospital with severe anæmia, and at the end of that time they still had high acid curves.

In seven cases of chlorosis there were two of hyperchlorhydria, two of high normal, one of normal and two of low normal curves. Excluding gastric ulcer, because here there are several possible factors at work, and splenic anæmia, in twenty-one other cases of anæmia there were two with hyperch'orhydria, three with high, five with normal, three with low normal curves, and eight with hypo- and achlorhydria. Most cases of hyperchlorhydria occurred among men, and of hypo- and achlorhydria among the women, but there are too few cases to generalise.

In Table IV the results are classified simply as high (including hyperchlorhydria and high normal), normal and low (including low normal hypo- and achlorhydria), and compared with Bell's findings (in percentages).

It is interesting that chlorosis and gastric ulcer show rather similar figures, the proportion of high curves being high in each case, but very much less so than in duodenal ulcer. In other anæmias the deviation from the normal is in the opposite

TABLE IV.

Disease.	Acidity of gastric contents.		
	High.	Normal.	Low.
Chlorosis	58	14	28
Addison's anæmia	0	0	100
Splenic anæmia *	0	0	100
Other anæmias	25	25	50
Normal students	26	59	16
Gastric ulcer	46	21	33
Duodenal ulcer	79	9	12

* Only three cases.

direction, a considerable number of curves being shifted from normal to low acidity.

Anæmia is generally associated with a diminution of gastric acidity, though achlorhydria is enormously less common than in Addison's anæmia or splenic anæmia, especially in men. In chlorosis, on the other hand, there is a tendency to increased secretion of acid.

Menstruation

The question of the menstrual periods in chlorosis is of great importance. Cabot states that in one-third there was amenorrhœa, in one-third the periods were scanty and irregular, and in one-sixth they were excessive. I do not think that in true chlorosis the periods are ever excessive, though they may often be described as regular or normal. Cases 120, 122 and 127 in the Appendix have been included to illustrate this. Case 120 had been treated for five years and was in hospital nine months before her anæmia was cured. Case 122 had been suffering in the same way for sixteen years, and even after this time her degree of anæmia was very slight. Case 127 had lost very large amounts of blood and was not cured by iron. It is generally agreed that menorrhagia may be made worse by iron, and these three are certainly not typical chlorosis and have only been included for comparison.

Of the rest there are notes about menstruation in 104 cases. In 21 it was not sufficiently abnormal to have drawn any attention. The others are difficult to classify, because frequently irregular periods were followed by amenorrhœa as the condition became worse. Taking the most striking symptom, there was amenorrhœa in 29 cases, and the periods were scanty or irregular or both in 54 cases. In the majority of these the periods had been irregular and scanty from the onset of puberty,

and there can have been much too little loss of blood to account for the condition as a simple secondary anæmia. Cabot quotes Von Noorden as saying that frequently menstruation had never appeared, but there are no notes of such a case in this series; though no doubt they occur, they cannot be very common. One can conclude that amenorrhœa or scanty or irregular periods occur in about 80 per cent. of the cases, and that this is one of the cardinal symptoms with breathlessness, weakness, constipation, indigestion and headaches, each occurring in three-quarters or more of the cases; and that œdema of the feet, fainting attacks and vomiting are less common symptoms, occurring in half of the cases, or rather less than this.

It is curious that Cabot found albuminuria in such a large percentage of his cases, for it is not referred to by Clifford Allbutt or Osler and was not mentioned in any case in this series. He also states that slight fever occurred in 90 per cent. If by slight fever is meant the evening rise of temperature to about 100°, which occurs so frequently in pernicious anæmia, it was certainly quite uncommon in this series.

Finally, there is a more serious complication. Thrombosis occurs in about 2 per cent. of cases (Cabot, v. Erben), and in a small proportion of these the cerebral sinuses are affected. There is no certain case of cerebral thrombosis in this series, but optic neuritis occurred in two cases (5, 19). Hawthorne [36] thinks that cerebral thrombosis may be the cause of some of these; otherwise the pathology is obscure. Retinal hæmorrhages occurred in Cases 30 and 128. A post-mortem examination was made in Case 22, without any very specific findings.

Treatment

There is little to say about treatment. It is certainly true that most cases can be cured rapidly by large doses of inorganic iron in many forms, but Bunge's suggestion of a strict control experiment where half the patients were treated with iron and half with similar dietetic measures without the iron has still to be carried out. The difficulties about the method of action of the iron have been admirably dealt with by Bunge,[32] and he summarises the experimental work on the subject, much of which was his own.

Anæmia can certainly be produced in animals by a continued use of a diet of low iron content, *e. g.* milk and bread. It can be produced almost if not quite as readily when the animals are given large doses of ferric chloride or other iron

salts. An anæmia so produced can be readily cured by adding to the diet articles containing large amounts of organic iron, *e. g.* meat, eggs and green vegetables; and not at all easily, if at all, by giving inorganic iron.

Moreover, iron given by mouth in man can be recovered almost quantitatively in the fæces. But Bunge admits that where large doses of iron are given by mouth, small amounts can be traced in the course of absorption, and as it is known that iron is almost entirely excreted by the intestine, it may be that the iron found in the fæces is not the same as the iron which was given by mouth, this having been absorbed in a form in which it can be utilised, and other iron which could not be utilised having been excreted by the large intestine.

This may be the explanation, though it does not seem very simple; or it may be that the iron is a specific stimulus to some gland of internal secretion whose function is deficient, or acts directly on some other organ.

One practical fact emerges. It would certainly be unwise to discontinue the use of inorganic iron in the forms in which experience is almost unanimous in its favour. It is equally clear that the diet should be changed to contain a maximum amount of organic iron, *e. g.* eggs, meat and green vegetables, and it is notorious that these substances are very deficient in the dietary of many chlorotics.

Prognosis

There is general agreement about the ease with which chlorosis can be cured and about the liability to relapse. Cabot says that of his 500 cases, 20 per cent. had had previous attacks, and of those who could be traced, 50 per cent. relapsed subsequently. At Guy's it has been more difficult to trace patients with chlorosis than those with several other diseases (*e. g.* exophthalmic goitre, gastric ulcer and Addison's anæmia). Of 11 severe cases in hospital in 1906–1907 only one could be traced, so that no attempt was made to follow up cases before 1909. After 1919 all patients but one could be traced, but it was not thought that long enough time had elapsed to obtain results of any special interest. Their state of health in 1923 is given in Table V. From 1909–1918 there were 37 cases, and only 14 of these could be traced. Most of them were nearly well and the majority were married. The details are given in the table.

TABLE V

AFTER HISTORY OF PATIENTS WHO COULD BE TRACED

Number.	Present condition (1922 or 1923).	Marriage and family.
56	Still suffers with breathlessness, constipation and œdema of the feet.	M. 1908; 2 children.
84	Slight constipation.	M. 1919; 1 child.
87	Slight breathlessness and œdema.	M. 1914; 3 children.
94	"Quite well."	
95	Slight indigestion and constipation.	M. 1920; no children.
97	Slight indigestion and breathlessness.	M. 1917; 3 children.
107	Healed phthisis R. apex. Constipation. Pale and weak since her baby was born. Hb. 70 %.	M. 1920; 1 child.
108	Constipation and headaches.	M. 1915; 3 children.
109	Practically well, but slight constipation.	Not married (1922).
112	Not anæmic; definite mental symptoms.	Not married (1923).
113	Well; slight breathlessness and constipation.	Not married (1923).
114	Still has indigestion, constipation and œdema.	M. 1918; 4 children.
115	Quite well except for headache and vomiting at monthly periods. Hb. 90 %.	Not married (1922).
116	Breathlessness, indigestion, vomiting and constipation.	Not married (1922).
119	Quite well.	M. 1920; 1 child.
*120	Relapsed 1921.	Not married (1923).
121	Quite well.	Not married (1923).
*122	Relapsed 1922.	Not married (1923).
124	Still has breathlessness, indigestion, constipation, œdema of the feet and irregular periods.	M. 1923.
125	Quite well.	Not married (1923).
*126	Better, but still pale and short of breath.	Married before admission.
*127	Relapsed 1922.	Not married (1923).
128	Extremely well.	Not married (1923).
129	Quite well.	Not married (1923).
130	Quite well.	Not married (1923).

* Not true chlorosis.

In a recent paper by Willebrand [24] the results of following up the patients from the Helsingfors Hospital are given in detail. Of 33 patients who could be traced, eight had died, five of phthisis and one of Graves' disease. Of the other 25, who were followed for an average period of more than fifteen years, blood examinations were made in 23. Fourteen of these were quite normal, and five only showed slight anæmia without severe symptoms referable to their anæmia. Of the four who had still severe anæmia, one had chronic uterine infection, one had developed a blood picture typical of Addison's anæmia, and in two no cause for the anæmia could be found.

Most of his paper is the detailed analysis of the symptoms from which they had suffered during these fifteen years.

Ten out of 25 had had more or less continuously symptoms referable to their heart without any evidence of organic disease of this organ. Half the patients continued to have gastric symptoms classified as hyper-acidity and secretion-neurosis, but only one had a definite gastric ulcer. More than half continued to have disturbances of menstruation, generally associated with pain. Only one had albuminuria.

Lloyd Jones, as a result of his studies of the specific gravity of the blood, suggested that chlorosis was a disease associated with unusual fertility. Neither this series nor Willebrand's lend any support to this theory. Of his patients, 11 were married and 14 were not, and of the married the average size of their family was four. Of this series nine were married and five were not; and the average size of the family was only two. So that both these series suggest that many chlorotics do not marry, and that if they do the family is not likely to be very large. Certainly the data on which this conclusion is based are very few.

The most interesting part of Willebrand's paper is his statement that 17 of the 25 had "greater or lesser degrees of the customary symptoms of a psycho-neurosis. Of these one developed severe hysteria and one a manic-depressive insanity. Scarcely one was without marked nervous disturbances at some period of her illness." He regarded this as some evidence in favour of Grawitz' view of chlorosis as a neurosis. It is an old view and de Sauvages spoke of *chlorose par amour*. But most writers have not found nearly such a close connection, and in this series such symptoms were not very evident, though they formed a prominent part of the picture in Case 30. Case 112 was interesting in this connection. She was in hospital with exophthalmic goitre in 1913, and was operated on by Mr. Fagge. In 1915 she was admitted under Dr. Fawcett with severe chlorosis, quite free from any symptoms of hyperthyroidism. Finally, last year she came under the care of Dr. Symonds at Out-patients with mental symptoms which almost required treatment in an asylum. But on the whole, taking the patients who could be traced, the great majority were able to lead a normal life and do their work, and were apparently free from severe anæmia, though they nearly all had still some symptoms, such as breathlessness, indigestion or constipation. The immediate results as judged by the patients who had been in hospital after 1919 were very much more satisfactory, but both this series and Willebrand's show that the ultimate prognosis is not as good as the immediate prognosis under the influence of iron.

Part IV. Discussion of the Etiology and the Causes of the Disappearance of Chlorosis.

The theories which have been put forward to account for chlorosis are very numerous and are generally lacking in experimental support. The arguments against the well-known ones of Virchow and Bunge are admirably stated by Clifford Allbutt,[16] and do not need any further mention.

Nor is the disease due to any excessive destruction of red cells, for what change there is seems to be in the other direction. There is no satisfactory evidence that constipation or intestinal toxæmia plays any part in its production.

There are two cardinal facts which must be taken into account in any explanation of the causation of chlorosis—the sex incidence and the age incidence. The disease is confined to women, for though a few authors have described cases of anæmia in boys as chlorosis, no series of cases has been substantiated, and most writers of experience agree that chlorosis does not occur in men. The age incidence is equally striking in all series which have been published and follows closely the onset of puberty. Cases occurring in older women are frequently relapses. Table VI shows the age incidence in this series of cases.

TABLE VI.

Age Incidence of Chlorosis

Age	12-13	14	15	16	17	18	19	20	21	22-24	25-27	28 and above
Cases	2	13	10	23	17	18	12	8	7	9	9	5

Cabot found 94 per cent. between 15 and 30, and Stockman 65 per cent. between 15 and 20, figures which agree well with this series.

These two factors suggest an etiology which is easy to understand on physiological principles—that anæmia follows the loss of menstrual blood, and that amenorrhœa is a secondary protective mechanism. The complete agreement of the blood picture in chlorosis and in a rapidly produced secondary anæmia is further evidence for this view. But there is one insuperable objection. In chlorosis it is very rare for the loss of blood to be excessive. Sometimes the monthly periods have never appeared and generally they have been scanty and irregular from the beginning.

It is true that sometimes the picture produced by menorrhagia is very similar to that of chlorosis, but the age incidence of menorrhagia is quite different, it is very difficult to cure and iron often does harm.

It might still be argued that the loss of blood in normal or even in smaller quantities than normal is too much for a badly developed and under nourished girl, but when the amount of blood lost at menstruation is considered, it is difficult to accept this explanation.

From this point of view it is interesting to consider the normal iron metabolism of the body. The blood and the liver contain the greater part of the iron, the blood containing about 2 grms. and the liver about a quarter of a gram. According to Stockman [21] on a normal diet the food contains about 10 mg. of iron daily, and of this 9 mg. are excreted in the fæces and 1 mg. in the urine. In the food of several chlorotics there was on an average only 2 mg. of iron, so that one source of the deficiency is revealed here, the excretion being normal in chlorosis and secondary anæmia, though it is raised to 8 or even to 10 mg. in the urine in Addison's anæmia (Hopkins).[22] For the total iron exchange it makes no difference whether all the iron taken in the food is excreted, and all the iron derived from the breakdown of red cells stored up and used for the formation of new red cells, or whether there is some exchange between these two sources. If the life of each red corpuscle is three weeks (Ashby [23]) there would be a daily destruction of red cells with an output of 100 mg. of iron. As only 10 mg. are excreted daily, most of this must be stored in the liver and used for the formation of new red cells. In the ordinary Blaud's pill there are 15 mg. of iron, and on Blaud's pill grs. x t.d.s. there would be a daily intake of nearly 100 mg. As it is generally necessary to give at least this amount of iron to cure chlorosis, it is rather suggestive that the daily breakdown of red cells is normal, but that in chlorosis the iron so set free cannot be used again and has to be replaced from an outside source.

Similar calculations are of interest in connection with menstruation as a cause of anæmia. Normally about 4 oz. of blood are lost at each period. This means 40 mg. iron for two or three days a month, an insignificant amount when the daily breakdown is remembered. But in excessive menorrhagia as much as 200 mg. may be lost, and if this continues for a long period, obviously a deficiency of iron may be produced.

What other factor might cause the tendency to anæmia at this time? Lloyd Jones' examination of the specific gravity

of the blood in chlorotics and in normal young women showed that the tendency to anæmia is widespread and occurs in 10 per cent. of women. There are many other changes, structural and functional, which take place at this time, and it is known that they depend on the internal secretion of the ovary. It is difficult to avoid the conclusion that the changes in the blood also depend on this, and the deficient menstruation suggests a deficiency of ovarian secretion, though the change might be qualitative rather than quantitative. Other investigations of the blood show that the anæmia is made much more severe by dilution of the blood, and there is some evidence that a loss of tone of the blood vessels under nervous influence or changes in the distribution of the blood are the cause of this. But here we are on less certain ground.

Causes of its Disappearance

The difficulty of drawing reliable conclusions from statistics is well known, but if the problem is approached with an open mind interesting correlations may sometimes be found. It has been shown by Ewart [6] and others that there is a close association between the decrease in the death-rate from phthisis and the increase in "real wages." * Both these processes have been taking place continuously and fairly steadily from 1830 to 1902, and there is a close parallelism between them. This is shown for the latter part of the period in Chart VII.

From 1902 to 1914 both these changes were almost arrested, and at the outbreak of the war the rise in prices caused an enormous drop in real wages (the subsequent rise in wages following behind the rise in prices), which is at once reflected in the increased death-rate from phthisis among the civilian population. Obviously many other factors are at work, but the correlation is so close that it seems very unlikely that it is due to coincidence.

It is difficult to know how closely the death-rate from phthisis depends on poor feeding, but Rowntree's figures as to the conditions of life in York make some connection easy to understand.[8] He found that in 1908 one-third of the population were living in poverty, and that in nearly half of these the poverty was so extreme that however economical the housewife

* "Real wages" represent the purchasing power of the average workman and so can be taken as a measure of his standard of living. They are obtained from the ratio of actual wages to the cost of food and other necessities. If the wages and prices of food and necessities for the decade 1898–1907 are both represented by 100, wages for 1878–1887 were 84 and prices 120, giving the figure 84 divided by 120, or 0·7 for "real wages"; and wages for 1888–1897 were 89 and prices 98·5, giving 0·9 for "real wages." [7]

and however coarse the food, no possible expenditure of the wages would have provided food of sufficiently high caloric value to reach Atwater's standards. Conditions in York were not peculiar, and were probably at least as good as those in Bermondsey. In the hospital reports of this period it is very frequent to read of conditions of extreme want approaching starvation. Case 30 in the Appendix, who returned to work with a hæmoglobin percentage of 20, and died the same day, within a few hours of her admission to hospital, can hardly be imagined at the present time.

It is often said that chlorosis is caused by hardship and poor feeding. Sir William Osler says that it occurs among "ill-fed, overworked girls of large towns, who are confined all day in close, badly lighted rooms. Cases occur, however, among the most favourable conditions, but not often in country-bred girls. Lack of proper exercise and fresh air and the use of improper food are important factors."

Some of these factors can be measured from known economic data and if chlorosis depends mainly on insufficient food, it would decrease as the standard of living increased. In Chart VII are shown the rise in real wages, the falling death-rate from phthisis, the decreased incidence of chlorosis, and the changes in unemployment. Unfortunately, for the greater part of the time no statistics about the incidence of chlorosis are available, and from 1888 to 1898 there are only figures for Guy's Hospital. These do show a general agreement with the phthisis mortality curve. But from 1898 to 1903 chlorosis was increasing while phthisis was decreasing. And from 1903 to 1914, when real wages and the phthisis death-rate were almost stationary, chlorosis was still decreasing. Again, at the beginning of the war chlorosis continued to decrease, but the phthisis death-rate increased enormously.

Perhaps there is some correlation between these two conditions, but it is certainly not a very close one and breaks down in detail, and the relationship suggests that the improved standard of living is only a small factor in the diminution of chlorosis.

During the middle of the nineteenth century, from 1830–1880, when the decrease in the phthisis death-rate was greatest, it is unlikely that there was much decrease in the amount of chlorosis. I do not know of any English figures bearing on this, but a comparison of Ashwell's cases in 1836 [4] with the Guy's cases of 1890 does not suggest much decrease. Cabot's figures [3] for America only refer to the end of the century, and the Swedish figures obtained since writing the above suggest

that it was actually increasing during this period. I do not know if the standard of living in Sweden was improving and the death-rate from phthisis diminishing as it was in England, but it is probable that these changes ran more or less parallel in the two countries.

These conclusions can be followed more clearly in Chart VII. The phthisis death-rate is taken from Ewart [6] and the figures for "real wages" from Wood,[10] and the latter have been

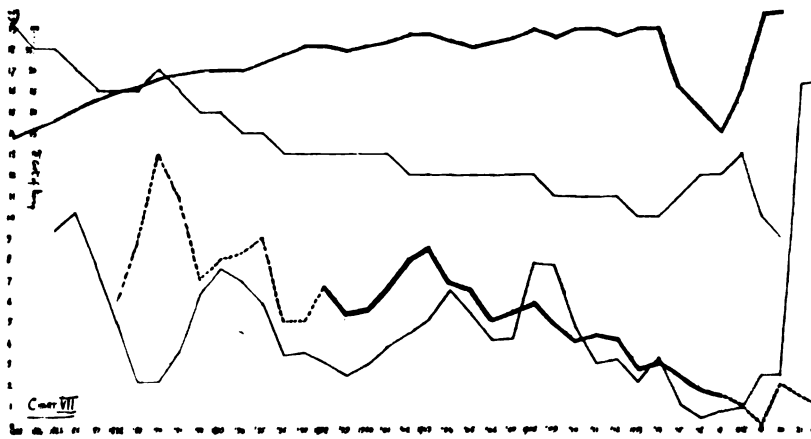

CHART VII.

INCIDENCE OF CHLOROSIS, DEATH-RATE FROM PHTHISIS, REAL WAGES, AND UNEMPLOYMENT (1883–1922).

The highest double line shows the improvement in the standard of living ("real wages").

The second line shows the decreasing death-rate from phthisis.

The third thick line shows the decreasing incidence from chlorosis—the dotted line being the figures for Guy's Hospital only.

The lowest line shows the changes in unemployment.

All curves except the cost of living are drawn against the same scale of figures.

checked and found to be in close agreement with the figures given by Beveridge in his standard book on unemployment.[7] The curve for the incidence of chlorosis is taken from the combined British figures for 1898–1917 and for Guy's Hospital only for the rest of the period. The figures for unemployment are taken from the official returns of all trade unions provided by the Ministry of Labour, and they have been compared with the similar figures given by Beveridge for part of the period [7] and by the report of the Royal Commission on the poor law.[9] If chlorosis were due to hardship and underfeeding, the amount of unemployment might give another means of testing this

hypothesis. It is true that this refers almost entirely to men's occupations, but periods of unemployment are usually times of general distress and privation. Again there is no very close correlation. It is tempting to connect the three peaks of 1894–1895, 1903 and 1908 with the unemployment of 1893–1894, 1904 and 1908–1909, but the greatest rise in chlorosis in 1890 corresponds with a time when there was very little unemployment, and the greatest rise in unemployment of 1921–1922 corresponds with a time when there was very little chlorosis. Finally, chlorosis has diminished throughout the period, while unemployment has shown large periodic fluctuations without any general tendency to rise or fall.

In conclusion a study of the cost of living and of unemployment does not suggest that hard conditions of life and poor food are the main factors in producing chlorosis, though both appear to have a slight influence on its incidence.

So much for the economic factors. No very close relationship has been found, and perhaps with a disease so sharply limited in its age and sex incidence it would be unlikely to find it closer. The social factors are much more difficult to estimate.

As regards occupation it is generally agreed that chlorosis is especially common among domestic servants. Cabot says that of his 500 cases 209 were among servants. In this series there were notes of the occupation in 53 cases. In thirty of these the patient was a servant and in five others a children's nurse or nursemaid, and in nine others the occupation was given as housework, which may, of course, have been at home. In only nine were the patients employed in other occupations, *e.g.* laundry workers, clerks, office cleaners or packers. Considering the comparative rarity of domestic service in Bermondsey and the large proportion of hospital patients who come from this area the figures are still more striking. Such an occupation can hardly be a direct cause. It is more likely that it acts indirectly by limiting the opportunity for fresh air and suitable exercise.

It seems very unlikely that servants as a class could be worse fed than girls of similar position employed in factory work. If there were any difference they should be better fed. There seems to be general agreement that about fifteen or twenty years ago the conditions of domestic service improved considerably, especially in the time which was to be spent out of the house. Such a conclusion is unsatisfactory, because it depends largely on personal impressions and no more definite data are available. But factory conditions can be studied

more easily, and these would have a direct influence on girls employed in factories and an indirect influence on the conditions of domestic service.

As it was difficult for me knowing the time of disappearance of chlorosis to collect data of factory conditions which could be regarded as quite unbiassed, I explained the general nature of the problem to my friends Mr. Leeson and Mr. Eagar, who have large practical knowledge of general social and legislative conditions, and asked them to let me know the time of the most important changes which might have affected the incidence of chlorosis. Mr. Eagar replied as follows:

"The important dates in legislation are really well before the beginning of the century; 1890 saw the Housing Act which gave the Borough Councils and L.C.C. wider powers to deal with insanitary houses, and should be taken in conjunction with the Public Health Act 1891 and its amendments of 1893, 1894, 1896, 1900, 1903 and 1906. The Housing and Town Planning Act 1909 further extended and consolidated housing legislation and in particular gave power to close underground rooms and enforced house-to-house inspection. The extent and efficiency of control of housing conditions was being extended all through the 1890–1900 period and there was an accumulative effect. 1891 was the year of a big Factory and Workshop Act which regulated hours and conditions and among other things prohibited the employment of women within four weeks after labour. There was another Act in 1905 and a general consolidating Act in 1901. In 1898 a Special Order under the 1891 Act prohibited taking meals in the parts of certain factories where specified processes were carried on, and the proper provision of sanitary appliances for both sexes was secured in London by a Public Health Amendment Act of 1890. The hours of employment of children were limited in 1891 and 1901. The 1901 Act generally speaking prohibited night work for women and young persons (*i. e.* under eighteen) and limited their hours to certain specified periods of the day. The 1903 Employment of Children Act extended the limitation of hours for children to all forms of employment besides those in factories. The 1901 Act required certificates of fitness for employment up to the age of sixteen in factories, and in 1907 this was extended to certain specified workshops.

"I feel that you will find it very hard to establish a clear connection between the diminution of the disease and any particular conditions, industrial or domestic, but there has been a piling-up of betterment factors; people in general are better clothed, better fed and more sanitarily lodged than they

were, women in particular are better protected than they were from the worst effects of industrial employment."

Mr. Leeson gave me a list of all legislation from 1888 to the present day which might have any bearing on the question, and from his list I have selected the following as the more important:

1890. Housing Act; Prevention of Infectious Diseases Act.
1891. Education Act (free elementary education); Factory and Workshop Act (regulating dangerous industries, ensuring fresh air, extending various conditions to women, etc.); Public Health Act.
1892. Shop Hours Act (limiting hours of employment of young persons to 74 hours a week.
1901. Factory and Workshop Act (mostly consolidation of old law).
1903. Employment of Children Act.
1904. Shop Hours Act (early closing).
1906. Education Act (provision of meals for necessitous children).
1907. Education Act (school medical service).
1908. Children Act (mainly consolidation).
1909. Trade Board Acts (minimum wage).
1911. Shops Act (weekly half holiday, rest hours for meals, etc.); National Sickness Insurance.
1913. Public Health Act (treatment of tuberculosis).

With such a mass of legislation affecting housing, factory conditions and other conditions, it is impossible to produce any proof of causal relationship. In such questions it is very difficult to distinguish *post hoc* and *propter hoc*. Moreover, the full effect of any special law may not be felt for several years, and frequently fresh regulations are made under the existing Acts.

But it is quite clear that throughout the period under review there has been a more or less continuous improvement in housing and in factory conditions, and it is the general impression that these improvements have been reflected in the conditions of domestic service.

The increased amount of fresh air and exercise taken by women and girls of the more educated classes is well known and this tendency is generally spreading. These changes have also taken place during the same period.

Certainly in making use of such general arguments it is difficult to carry conviction, but after considering various possible hypotheses I have come to the conclusion that the

disappearance of chlorosis is a very real change, and that it is mainly due to improved conditions of employment allowing more opportunity for fresh air and exercise. It should be possible to test such a hypothesis by comparing the amount of chlorosis among the class of Turkish women living in close confinement and among the peasant women of the other Balkan states where most other conditions are fairly similar. Possibly some doctors with experience of the Near East could provide such information, but I have not been able to find it.

While talking on the subject with Mr. Leeson, he suggested that the disappearance of chlorosis and the whole women's movement of the last generation were due to the same cause, to an inborn, rather than to an environmental change. Such an idea is interesting, but there is little known about evolutionary changes and it seems much more likely that what changes there are, both physically and in other spheres, are due to changes in environment and education.

The main interest of the Swedish figures is that while on the whole supporting the English figures for the disappearance of chlorosis, they provide some evidence of its previous increasing incidence and rather suggest a periodic change. But perhaps while general conditions of life were improving, the conditions of women's employment and activity were not improving. The general picture of women's life in the Victorian age in England rather supports this view.

I have no means of deciding whether this decrease in Sweden supports in any way the theories which I have put forward very tentatively. On the whole it seems rather unlikely that social changes and legislation would run so closely parallel in the two countries and these would probably not vary by so many years in different towns. It seems possible, but unlikely that there is some general cause with a definite periodicity at work, as in the epidemic of infectious diseases, though the whole evidence is against any infective agency in chlorosis.

Schauman discusses the causes of the changed incidence at some length, but without any very definite conclusions. He is rather inclined to attribute it to alcoholism in the parents, for the consumption of alcohol per head of the population increased in the earlier part of the period considerably and decreased enormously in the latter part of the period. But it was a regular and gradual change, unlike the incidence of chlorosis. Moreover the disappearance of chlorosis preceded prohibition in America. He ends with the unsatisfactory but perhaps necessary conclusion "in generandis morbis non una, sed plures concurrunt causæ."

It may be urged against this view that chlorosis is a disease almost entirely confined to young women, and that the general conditions discussed apply to all women. But they certainly apply with much less force to married women not at work, for they must generally spend a part of each day in the open air in their ordinary household duties. In the figures of Guy's and St. Bartholomew's Hospitals anæmia is much more common among women than among men at all ages. The cases at Guy's Hospital indexed as anæmia are drawn in Chart I and show some general correlation with the various factors discussed, though this is not as close as in the cases of chlorosis.

It is always rather unsatisfactory when several causes have to be used as an explanation, but in the known infectious diseases, *e. g.* tuberculosis or even typhus fever, other factors are of considerable importance in the etiology. It seems that chlorosis is made possible by the changes which take place normally at puberty, and perhaps to a lesser extent later in life, but that it only develops to a noticeable extent where the environment, especially the amount of fresh air and exercise, is unsatisfactory.

I am deeply indebted to Professor A. J. Hall and Sir William Hale White for their help and criticism. This paper could hardly have been written without them, and Professor Hall collected many of the data dealing with the disappearance of chlorosis. I also wish to thank Mr. Eagar and Mr. Leeson for their help with the latter part of the paper on social and economic factors.

Conclusions

1. Taking all British hospitals whose statistics have been examined, chlorosis decreased steadily from 1903 to 1918; in individual hospitals the decrease was generally more sudden at some particular part of the period. It applies equally to In-patients and Out-patients. Very little, if any, of the decrease can be accounted for by changes in the use of the word chlorosis or by improved methods of diagnosis. In 1916 the number of cases was only half the number in 1910, and less than a quarter of the number in 1903. There is no evidence that the war was in any way the cause of this decline. In the years before the war the decrease was just as rapid, and it was equally marked in a neutral country, *i. e.* Sweden.

2. From 1899–1903 there was an increase, but it was not very great and was balanced by the decrease from 1903–1906, since when it has been at a level lower than any previously recorded.

3. There are not enough figures available before 1898 to draw equally certain conclusions, but at Guy's there was a big decrease from 1890–1899. Except for a slight increase during four years, there has been a steady decrease for more than the last thirty years.

4. In America and Sweden there has been a similar decrease, but some of the older Swedish figures suggest that many years of increase preceded the decline. Apart from this, all the other evidence is against a periodicity in the incidence of chlorosis.

5. There is good evidence that improved conditions of factory life and domestic service are the main cause of the decrease. Probably these act by giving opportunities for more fresh air and exercise. Lack of food, or at any rate of food containing sufficient iron, may be an additional factor, but this does not seem to be equally important.

6. The colour-index and size of the red cells diminish regularly as the hæmoglobin percentage becomes lower. Both these changes are exactly the same as in secondary anæmia. Splenic anæmia occupies an intermediate position between these and Addison's anæmia.

7. Changes in the blood volume intensify the anæmia, even if they are not the main cause of it. This may partly depend on a loss of tone of the capillaries and smaller vessels, but this remains unproved.

8. The changes in the specific gravity of the blood in chlorotics and in other girls show that chlorosis is only an exaggeration of a physiological change which occurs in at least 10 per cent. of women at puberty.

9. This fact and the age and sex incidence show that the tendency to anæmia is part of the change associated with the onset of puberty. As all the other changes at this time depend on the internal secretion of the ovary, it is difficult to avoid the conclusion that chlorosis also depends on changes in the ovary and that it should be considered with diseases of the ductless glands.

10. Although the great majority of cases occur after menstruation has started, the periods are generally scanty and irregular from the beginning, and the loss of blood cannot explain the anæmia. Amenorrhœa is a symptom of chlorosis rather than a protective mechanism, and this suggests deficient ovarian activity.

11. In chlorosis there is a tendency to increased secretion of HCl in the gastric juice, as opposed to the generally diminished acidity in most other anæmias and the absent acidity in Addison's anæmia.

12. There is no evidence of any association between gastric ulcer and chlorosis as judged by the after histories of these patients and of Willebrand's series, though symptoms of indigestion may persist for a long time.

13. Although the immediate symptoms are readily cured with iron, many of the symptoms of chlorosis continue intermittently for many years, if not through life.

APPENDIX OF CASES OF CHLOROSIS

Cases of Chlorosis treated in Guy's Hospital during the Year 1890 under Dr. Pavy, F.R.S., Dr. Pye Smith, F.R.S., Sir Frederick Taylor and Sir James Goodhart.

(43 cases are diagnosed in the index of diseases as chlorosis, but a summary is only given here of 21 cases with a percentage of hæmoglobin of 50 and under, and of 9 cases where the clinical symptoms were those of chlorosis in its present meaning, no blood count being available.)

*1. ♀ 18 yrs.; *needlework.* Admitted for fainting, headaches, anæmia and constipation. Red cells 3·0 millions, hæmoglobin 30 per cent. Periods started at 15 and were regular. At first there was a very slow improvement with hydrochloric acid, afterwards a rapid improvement with iron, the Hb. rising to 95 per cent.

2. ♀ 19 yrs.; *housework.* Admitted for breathlessness, headaches, vomiting and indigestion. Periods began at 15 and were scanty and irregular.

3. ♀ 17 yrs.; *housework,* poor home surroundings. Admitted for anæmia, vomiting and amenorrhœa. Chorea at 6 years. Periods began at 16; three months' absence before admission.

4. ♀ 20 yrs.; *housework.* Admitted for breathlessness for four years and more recent œdema of the feet. Periods began at 14 and were regular.

*5. ♀ 19 yrs.; *servant.* Admitted for faintness, anæmia and blurred vision. Red cells 3·3 millions, Hb. 42 (? early optic neuritis). Periods began at 17 and were irregular.

*6. ♀ 18; *nursemaid.* Admitted for indigestion, headaches and pains in the legs. She was pale, breathless and constipated, with slight œdema of the feet. Red cells 2·1 millions.

7. ♀ 20; *housework.* Admitted for breathlessness and indigestion. Periods began at 12 and were regular for two years, and afterwards irregular and scanty. Red cells 1·0 million, Hb. 20 per cent. She was still very anæmic on discharge. (The cause of this anæmia was doubtful, as the

colour-index was high and she did not improve rapidly with iron.)

*8. ♀ 20; *housework.* Admitted for weakness, constipation and irregular appetite. Periods began at 14 and were irregular and scanty. Red cells 1·6, Hb. 25. The red cells rose to six millions.

*9. ♀ 17; *servant.* Admitted for weakness and giddiness. She was constipated and had indigestion. Periods began at 15 and were irregular and scanty, and more recently absent. Red cells 3·5, Hb. 42.

*10. ♀ 17; *office cleaner.* Admitted for breathlessness, headaches, fainting and œdema of the feet. She used to have indigestion and constipation. Periods began at 14 and were regular but scanty. Red cells 3·5, Hb. 35. Her red cells rose to 6 millions.

11. ♀ 18; *nursemaid.* Admitted for anæmia and debility. She was constipated and had indigestion. Periods began at 15 and were irregular and scanty.

*12. ♀ 17; *servant.* Admitted for anæmia, headaches, weakness and indigestion. Red cells 4·9, Hb. 50.

13. ♀ 25; *housemaid.* Admitted for pains in the legs, headaches and weakness. She was very short of breath and had recently developed œdema of the feet. Periods began at 13 and were regular until five months before admission, when they ceased.

14. ♀ 20; *packer.* Admitted for shortness of breath, weakness and palpitation. Periods began at 16 and were for a year before admission irregular and scanty.

15. ♀ 28; *housework.* Admitted for two years' anæmia, palpitation and breathlessness. Periods began at 13 and had been irregular and scanty for four years.

*16. ♀ 22; *servant.* Admitted for breathlessness, headaches, fainting and precordial pain. She had had two previous attacks. Her periods were regular but scanty. Red cells 3·2, Hb. 45.

*17. ♀ 20; *servant.* Admitted for breathlessness, precordial pain and indigestion for two years. Red cells 3·3, Hb. 25.

*18. ♀ 20; *servant.* Admitted for headaches, breathlessness, anæmia and œdema of the feet. Periods were irregular and scanty. She had been in hospital once before for a similar attack. Red cells 3·2, Hb. 25.

*19. ♀ 19; *servant.* Admitted for weakness, sickness, headaches and failing eyesight. She was said to be half-starved. Periods had been absent for three months and irregular for six months previously. The eyesight had been failing for six days. Red cells 3·0, Hb. 50. There was double optic neuritis. Red cells rose to 4·8 millions and her eyesight and general condition were both much improved.

*20. ♀ 17; *servant.* Admitted for breathlessness, headaches and fainting. Periods started at 14 and were regular. Red cells 5·0, Hb. 35.

*21. ♀ 24; *servant.* Admitted for breathlessness, palpita-

tion, vomiting and constipation. Periods began at 15 and were regular until six months before admission. Red cells 3·5 millions.

*22. ♀ 18; *waitress.* Admitted for extreme weakness. She had been ill for three or four weeks after "influenza." During this illness there were pains in the joints and her knees were swollen at one time, so it is difficult to exclude rheumatic fever. She was very short of breath, and had no gastro-intestinal symptoms. On the morning of her admission she returned to work, much against her doctor's advice. She collapsed at work and was brought up to hospital in a cab. Red cells were 4·8 millions and Hb. was only 20 per cent. She died a few hours after admission. POST-MORTEM: Her heart was slightly dilated; there was a little fluid in the pleural cavity, and extreme anæmia. No other cause for death could be found.

*23. ♀ 18; *servant.* Admitted with two years' history of anæmia, breathlessness and indigestion. Recently she had started vomiting, and œdema of the legs had developed. Red cells 2·8, Hb. 30.

*24. ♀ 21; *housemaid.* Admitted for breathlessness, headaches, giddiness, œdema of the feet and a greenish colour of the skin. Periods started at 17 and were irregular and scanty. Red cells 3·7, Hb. 21.

*25. ♀ 18; *laundress.* Admitted for breathlessness, palpitation and œdema of the legs. Periods began at 14 and were always irregular and stopped four months before admission. She had several similar attacks previously, but with the last attack had indigestion and vomiting. Red cells 2·5, Hb. 42. Blood count on discharge: red cells 5·1, Hb. 60.

*26. ♀ 22; *servant.* Admitted for breathlessness, weakness and fainting attacks. She had had two attacks previously, and was said to have been very short of food from 14 to 17. Periods began at 15 and were regular, but scanty and painful. Red cells 3·6, Hb. 30 on admission, 64 on discharge.

27. ♀ 26; *servant.* Admitted for lassitude, anæmia, headaches and constipation. Her periods were regular.

28. ♀ 21; *housemaid.* Admitted for breathlessness, abdominal pain, constipation and sickness. Periods started at 14 and were irregular and scanty for six months before admission.

*29. ♀ 18; *nursemaid.* Admitted for weakness, constipation and sickness. Her periods began at 15 and were irregular and scanty, but on the whole rather frequent. Red cells 3·5.

*30. ♀ 20; *servant.* Admitted for weakness, anæmia and œdema of the feet. Her periods started at 12 and were regular. She was quite well in the country, but had been often "hysterical" since coming to London two years previously. Red cells 4·4, Hb. 43. She had severe neuralgia and retinal hæmorrhages in both eyes.

CASES OF CHLOROSIS TREATED IN GUY'S HOSPITAL DURING THE YEAR 1908 UNDER SIR WILLIAM HALE WHITE, DR. SHAW, DR. NEWTON PITT AND SIR COOPER PERRY.

(31 cases are diagnosed in the index as chlorosis, but a summary is only given here of 15 cases with a hæmoglobin percentage of 65 or under, and of 6 cases where the symptoms were those of chlorosis in its present meaning, no blood count being available.)

*60. ♀ 18; *parlourmaid.* Admitted for anæmia and breathlessness for a year. Red cells 6·0, Hb. 65.

61. ♀ 21; *servant.* Admitted for constipation, indigestion and anæmia. Periods regular.

*62. ♀ 16; *rice-packer.* Admitted for six months' weakness, giddiness and loss of appetite, and one month's vomiting. Red cells 2·5, Hb. 30. Rapid improvement.

*63. ♀ 16; *confectionery shop.* Admitted for three years' increasing anæmia, sickness, constipation and fainting attacks. Red cells 3·8, Hb. 60.

64. ♀ 23; *housemaid.* Admitted for anæmia, constipation, epigastric pain and vomiting. Periods began at 13 and were irregular and scanty. She had a hæmatemesis at 13, but no similar trouble since. She had been anæmic for five years.

*65. ♀ 21; *housemaid.* Admitted for anæmia, palpitation, fainting and constipation. Periods irregular and scanty. Slight pyrexia. Red cells 3·5, Hb. 50.

66. ♀ 17; *nurse.* Admitted for breathlessness, anæmia and headaches. Bowels regular. Periods regular but scanty.

*67. ♀ 25; *servant.* Admitted for one year's breathlessness and œdema of the feet. Periods scanty and irregular. Slight pyrexia. Red cells 4·3, Hb. 30 on admission, 74 on discharge.

68. ♀ 19; *servant.* Admitted for pallor, breathlessness, indigestion, vomiting and œdema of the feet. Periods regular but scanty.

*69. ♀ 17; *servant.* Admitted for breathlessness, anæmia and indigestion. Periods began at 14 and were irregular and scanty. Red cells 3·8, Hb. 45. Rapid improvement.

*70. ♀ 16; *clothes sorter.* Admitted for headaches, giddiness, vomiting and indigestion. Periods began at 14 and were always irregular and scanty, and absent for eight months before admission. Slight pyrexia. Red cells 4·4, Hb. 60.

*71. ♀ 32; *nurse.* Admitted for five years' history of anæmia and severe constipation, and more recent breathlessness and œdema of the feet. Red cells 4·2, Hb. 55. Periods irregular.

72. ♀ 27; *clerk.* Admitted for constipation, breathlessness, œdema, vomiting and indigestion. Periods irregular. Red cells 4·2, Hb. 55. At a laparotomy no evidence of a gastric ulcer could be found. The pathology of this case was obscure, especially as the fæces were bulky and consisted almost entirely of fat.

*73. ♀ 21; *cook*. Admitted for indigestion, vomiting, breathlessness and œdema. Periods started at 12 and had always been irregular, and absent for two years. Slight pyrexia. Red cells 4·6, Hb. 48.

*74. ♀ 22; *parlourmaid*. Admitted for weakness, breathlessness, loss of appetite and constipation. She had had two previous attacks of anæmia. Periods regular and normal. Red cells 3·4, Hb. 58 on admission, 92 on discharge.

*75. ♀ 18; *servant*. Admitted for breathlessness and indigestion. Periods began at 14 and were scanty and irregular. Red cells 4·0, Hb. 25. Rapid improvement.

*76. ♀ 32; *cook*. Admitted for breathlessness, palpitation and œdema for four years. Bowels regular. Periods irregular. Slight pyrexia. Red cells 3·0, Hb. 50. Rapid improvement.

*77. ♀ 26; *housework*. Admitted for indigestion, vomiting, breathlessness and constipation. She had been anæmic since 17. Red cells 4·5, Hb. 58. Rapid improvement.

*78. ♀ 19; *servant*. Admitted for breathlessness, œdema and amenorrhœa. Slight pyrexia. Red cells 5·4, Hb. 35. Rapid improvement.

79. ♀ 20; *servant*. Admitted for constipation, indigestion, occasional vomiting and anæmia. Periods regular.

80. ♀ 15; *cutter*. Admitted for anæmia, headaches, breathlessness and fainting attacks. Periods began at 14 and were very irregular.

CASES OF CHLOROSIS TREATED IN GUY'S HOSPITAL DURING THE YEARS 1920, 1921 AND 1922 UNDER DR. FAWCETT, DR. BEDDARD, DR. HURST AND DR. FRENCH.

(13 cases were indexed as chlorosis; of these 9 would be diagnosed chlorosis in its present sense.)

*118. ♀ 16; *servant*. Admitted for breathlessness, giddiness and headaches. She was constipated in hospital. Periods began at 15 and were regular at first, but had been absent for some months. Slight œdema of the feet was present, and there was low pyrexia for about a week. Red cells 4·0, Hb. 30 on admission, 78 on discharge.

*119. ♀ 20; *housework*. Admitted for breathlessness, headaches and dizziness. Her appetite was good but she was constipated. Periods were regular but scanty. Her colour was greenish. Red cells 4·8, Hb. 48 on admission, 68 on discharge. She was married some months after discharge, and when seen eighteen months later she was quite well; her hæmoglobin percentage was 82, but she still looked greenish. Her sister was under treatment for chlorosis. Her fractional test-meal showed a high normal curve while she was in hospital.

120. ♀ 23; *cook*. Admitted for weakness, breathlessness and severe anæmia. She was constipated but had no indigestion. Her periods began at 15 and were regular and rather

excessive, always leaving her with lassitude and increased dyspnœa for about a week. She had been under treatment intermittently for five years. Red cells were 2·2, and Hb. was 19, and four months later, after vigorous treatment, the red cells were only 3·5 and Hb. 28. It is not clear from the report if large doses of Blaud's pill were ever used, but injections of organic iron preparations and novarsenobenzol were used extensively. No specific cause for the anæmia could be found. Her Wassermann reaction was negative, no ova could be found in the fæces and differential counts were normal. Only five normoblasts were found in many blood films, and except for slight aniso- and poikilocytosis there was no other abnormality of the red cells. Ultimately, after removal of her tonsils and some teeth and treatment with a mixed vaccine containing Strept. longus and Micrococcus catarrhalis prepared from her teeth, she improved greatly, and her hæmoglobin percentage rose to 70 after she had been in hospital nearly six months.

Five months later her symptoms recurred, and as her Hb. was only 48 she was re-admitted. She improved rapidly with Blaud's pill in increasing doses, her Hb. rising to 80.†

*121. ♀ 18. Admitted for six months' breathlessness, giddiness, œdema of the feet and indigestion. Her periods began at 16 and were absent for a few months before admission. Red cells 2·5, Hb. 30 on admission, 65 on discharge. Two years later she wrote that she was at work and quite well.

122. ♀ 32. Admitted for breathlessness and fainting attacks from which she had suffered intermittently for sixteen years. Her periods began at 16 and were regular and rather excessive. She had œdema of the feet and a little indigestion, but was not constipated. Two years later she was seen and was quite well except for a little shortness of breath. Her hæmoglobin percentage was 78.†

123. ♀ 19. Admitted for breathlessness, indigestion and constipation. Her periods were scanty and she looked anæmic. She improved rapidly. A fractional test-meal gave a low normal curve.

*124. ♀ 32. Admitted for six years' history of headaches, lassitude and fainting attacks, and more recently vomiting and indigestion. Periods began at 14, were scanty and irregular but rather excessive before admission. Red cells 4·6, Hb. 46. She improved rapidly, but was not cured two years later, still having breathlessness, constipation and slight indigestion, especially if she took meat.

*125. ♀ 19. Admitted for breathlessness, headaches, giddiness and indigestion. Her colour was yellowish-green. Her bowels were regular. Her periods began at 16, and were regular, but absent for some months before admission. Red cells 5·1, Hb. 30 on admission, 75 on discharge. Two years later she was quite well.

126. ♀ 29; married; four children. Admitted for increasing breathlessness and anæmia during pregnancy. Red cells 3·0, Hb. 32 on admission, 75 on discharge. Some septic teeth

were removed while she was in hospital. A month after discharge an abortion took place. A year later her Hb. was 65. She was well except for breathlessness, but looked pale and sallow and more like some form of infection than typical chlorosis.†

127. ♀ 13. Admitted for weakness and breathlessness. Her periods started at 12 and were irregular and very excessive, leaving her pale and weak. Red cells 2·4, Hb. 25 on admission, 56 on discharge. A year later she still lost unusual amounts of blood each month and was weak and pale (Hb. 60).†

*128. ♀ 20. Admitted for two months' history of extreme breathlessness and weakness. Her periods which had been regular had stopped for two months. There was slight œdema of the ankles and she saw red spots whenever she looked at anything. Red cells 1·8, Hb. 25 on admission, 60 on discharge. There were retinal hæmorrhages in both eyes. No cause for the anæmia could be found. She improved rapidly with Blaud's pills and was quite well a year later, when her hæmoglobin percentage was 78. A fractional test-meal was normal.

*129. ♀ 22. Admitted for giddiness, fainting and breathlessness. Periods started at 15 and were regular but scanty. Her colour was greenish. Red cells 4·8, Hb. 50 on admission, 74 on discharge. A fractional test-meal gave a low normal curve. A year later she felt well but still looked greenish.

*130. ♀ 18. Admitted for breathlessness, œdema, indigestion and constipation. Periods had always been scanty and she had had amenorrhœa for some months. Red cells 4·2, Hb. 40 on admission, 72 on discharge.

* = cases "proved" by blood examination.
† = not true chlorosis.

TABLE VII

CASES OF CHLOROSIS TREATED AT GUY'S HOSPITAL DURING THE YEARS 1890 AND 1906–1922.

Number.	Age at onset.	Age on admission.	Red cells (millions).	Hæmoglobin.	Colour-index.	Breathlessness.	Œdema of feet.	Fainting.	Indigestion.	Constipation.	Periods.	
1	—	18	3·0	30	0·5	+		+		+	regular	1890
2	17	19	—	—	—	+			+		scanty	
3	16	17	—	—	—	+			+	+	amenorrhœa	
4	—	20	—	—	—	+	+				regular	
5	17	19	3·3	42	0·6	+		+		+	irregular	
6	—	18	2·1	—	—	+	+		+	+	—	
7	14	20	1·0	20	1·0	+			+		irregular	
8	16	20	1·6	25	0·7	+			+	+	irregular	
9	15	17	3·5	42	0·6	+			+	+	amenorrhœa	
10	16	17	3·5	35	0·5	+	+	+	+	+	scanty	
11	15	18	—	—	—	+			+	+	irregular	
12	—	17	4·9	50	0·5	+			+		—	
13	—	25	—	—	—	+	+		+		amenorrhœa	
14	17	20	—	—	—	+				+	irregular	
15	21	23	—	—	—	+		+		+	scanty	
16	16	22	3·2	45	0·7	+		+			scanty	
17	18	20	3·3	25	0·4	+			+		—	
18	17	20	3·2	25	0·4	+	+			+	irregular	
19	18	19	3·0	50	0·8	+			+	+	amenorrhœa	
20	—	17	5·0	35	0·3	+		+			regular	
21	23	24	3·5	—	—	+			+	+	amenorrhœa	
22	18	18	4·8	20	0·2	+					—	
23	16	18	2·8	30	0·5	+	+		+		—	
24	18	21	3·7	21	0·3	+	+	+		+	scanty	
25	15	18	2·5	42	0·8	+	+		+	+	amenorrhœa	
26	—	22	3·6	30	0·4	+		+		+	scanty	
27	—	26	—	—	—	+				+	regular	
28	20	21	—	—	—	+			+	+	irregular	
29	15	18	3·5	—	—	+			+	+	irregular	
30	18	20	4·4	43	0·5	+		+		+	regular	
31	16	22	—	—	—	+		+	+		irregular	1906
32	20	21	5·1	60	0·6	+	+			+	irregular	
33	14	16	—	—	—		+		+	+	—	
34	16	19	4·2	40	0·5	+	+	+		+	amenorrhœa	*
35	16	18	4·0	50	0·6	+			+	+	irregular	
36	16	20	3·8	44	0·7	+	+			+	irregular	*
37	21	22	3·5	30	0·4	+		+			irregular	
38	14	17	4·0	60	0·7	+			+	+	—	
39	26	27	—	—	—	+			+	+	—	
40	15	21	—	50	—	+	+	+	+	+	—	
41	18	19	3·8	41	0·5	+			+		regular	*
42	24	25	5·0	60	0·6		+		+	+	irregular	

Number.	Age at onset.	Age on admission.	Red cells (millions).	Hæmoglobin.	Colour-index.	Breathlessness.	Œdema of feet.	Fainting.	Indigestion.	Constipation.	Periods.	
43	16	17	5·0	60	0·6	+			+	+	irregular	1907
44	17	19	5·0	38	0·4			+	+	+	amenorrhœa	
45	29	31	6·0	55	0·4	+	+				regular	*
46	17	20	—	—	—	+	+			+	—	
47	22	23	—	—	—	+			+	+	irregular	
48	—	18	4·7	45	0·5			+	+		regular	*
49	—	17	3·3	35	0·5	+				+	amenorrhœa	*
50	21	22	3·8	50	0·7	+			+	+	irregular	*
51	14	14	4·9	65	0·6	+		+	+	+	—	
52	17	20	3·3	50	0·8	+	+		+	+	irregular	*
53	20	22	—	—	—	+				+	—	
54	—	21	—	—	—	+	+		+	+	—	
55	—	19	6·4	50	0·4	+			+	+	irregular	*
56	16	21	3·7	42	0·5	+	+	+	+	+	amenorrhœa	‡
57	19	20	3·7	32	0·4	+			+		irregular	*
58	14	17	4·1	40	0·5	+	+		+	+	regular	
59	—	28	4·0	60	0·7	+			+	+	regular	
60	17	18	6·0	65	0·5	+	+				—	1908
61	—	21	—	—	—	+			+	+	regular	
62	16	16	2·5	30	0·6	+		+	+		—	
63	13	16	3·8	60	0·7	+		+	+	+	irregular	
64	18	23	—	—	—	+			+	+	irregular	
65	—	21	3·5	50	0·7	+		+		+	irregular	
66	16	17	—	—	—	+	+				regular, scanty	
67	24	25	4·3	30	0·4	+	+			+	irregular	
68	—	19	—	—	—	+	+		+		regular, scanty	
69	14	17	3·8	45	0·6	+	+		+		irregular	
70	14	16	4·4	60	0·7				+	+	amenorrhœa	
71	27	32	4·2	55	0·7	+	+			+	irregular	
72	—	27	4·2	55	0·7	+	+		+	+	irregular	
73	19	21	4·6	48	0·5	+	+		+		amenorrhœa	
74	17	22	3·4	58	0·8	+			+	+	regular	
75	15	18	4·0	25	0·3	+		+	+		irregular	
76	28	32	3·0	50	0·8	+	+				irregular	
77	17	26	4·5	58	0·7	+			+	+	—	
78	—	19	5·4	35	0·3	+	+				amenorrhœa	
79	—	20	—	—	—	+			+	+	regular	
80	14	15	—	—	—	+	+	+			irregular	
81	17	17	4·1	40	0·5	+		+		+	scanty	1909*
82	25	28	4·0	60	0·7				+	+	regular	*
83	14	15	3·4	40	0·6	+		+			scanty	*
84	16	17	4·1	50	0·6	+	+			+	amenorrhœa	‡
85	21	22	5·0	55	0·5	+	+				irregular	*
86	19	20	2·5	45	0·9	+			+	+	regular	‡
87	18	20	3·9	35	0·4	+		+		+	irregular	1910‡
88	18	25	3·9	40	0·5				+	+	regular	*
89	17	18	3·5	30	0·4	+			+	+	scanty	*
90	18	21	3·2	35	0·5	+	+	+			amenorrhœa	*

Number.	Age at onset.	Age on admission.	Red cells (millions).	Hæmoglobin.	Colour-index.	Breathlessness.	Œdema of feet.	Fainting.	Indigestion.	Constipation.	Periods.	
91	26	27	4·4	60	0·7	+		+	+	+	—	1911*
92	14	15	5·5	50	0·5	+		+			scanty	*
93	18	22	5·2	50	0·5	+	+	+	+	+	regular	*
94	16	18	3·2	45	0·7	+				+	irregular	‡
95	17	19	4·0	55	0·7	+	+	+			amenorrhœa	‡
96	16	17	3·9	45	0·5	+	+		+		amenorrhœa	*
97	21	23	4·0	50	0·6	+			+		amenorrhœa	‡
98	21	23	4·1	60	0·7	+			+		—	1912*
99	15	16	4·8	60	0·6		+		+	+	scanty	*
100	29	30 m.	2·8	40	0·7	+	+				regular	*
101	14	42 m.	4·2	40	0·5	+	+			+	—	*
102	18	20	4·1	40	0·5	+			+	+	—	1913*
103	15	16	3·2	20	0·3	+	+	+	+	+	amenorrhœa	*
104	22	23 m.	4·2	50	0·6	+			+		scanty	*
105	15	17	3·2	45	0·7	+	+	+	+	+	irregular	*
106	18	20	4·7	55	0·6	+				+	—	1914*
107	17	18	4·4	40	0·5	+			+	+	scanty	‡
108	22	23	3·1	32	0·5	+	+	+	+		scanty	‡
109	25	26	3·5	38	0·5	+				+	irregular	‡
110	16	18	3·5	60	0·9				+	+	—	1915*
111	14	15	4·5	55	0·6	+			+		—	*
112	14	15	3·2	40	0·6	+	+	+	+		—	
113	19	20	3·4	30	0·4	+	+				irregular	1916†‡
114	—	32	4·8	60	0·6		+		+	+	irregular	1917†‡
115	20	21	3·5	60	0·9	+			+	+	amenorrhœa	‡
116	19	24	4·1	51	0·6	+			+	+	regular	‡
117	19	20	3·1	—	—	+	+			+	irregular	1918*
118	15	16	4·0	30	0·4	+	+			+	amenorrhœa	1920*
119	19	20	4·8	48	0·5	+				+	scanty	‡
120	18	23	2·2	19	0·4	+	+			+	regular +	†‡
121	17	18	2·5	30	0·6	+	+	+	+		amenorrhœa	‡
122	16	32	5·8	68	0·6	+		+	+	+	excessive	†‡
123	16	19	—	—	—	+			+	+	scanty	*
124	26	32	4·6	46	0·5	+	+	+	+	+	irregular	1921†‡
125	18	19	5·1	30	0·3	+			+		amenorrhœa	‡
126	29	29	3·0	32	0·5	+	+			+	regular	†‡
127	12	13	2·4	25	0·5	+	+	+		+	excessive	†‡
128	20	20	1·7	25	0·7	+	+			+	amenorrhœa	1922†‡
129	21	22	4·8	50	0·5	+		+		+	scanty	‡
130	18	18	4·2	40	0·5	+	+		+	+	amenorrhœa	‡

* = could not be traced. † = not true chlorosis. ‡ = traced; see Table V.

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STUDIES ON TUMOUR FORMATION

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VII. THE HETEROTOPIC TUMOURS

Nature is ultra-conservative in most of her affairs, but when she sets out on a new venture—she throws tradition to the winds.—SIR ARTHUR KEITH.[33]

I HAVE hitherto in these studies used, with but few exceptions, tumours whose cells possess the same structure as those of the tissues in which they are found. In the case of the examples discussed in Study V. there is good evidence to show that they have originated in dislocated cells and in accessory organs, with whose epithelium they are usually identical in structure. When marked differences are present, as in the melanomata and the hypernephromata, these are, as I have attempted to show, merely secondary, depending upon degenerative changes undergone by the cells of the neoplasm. It can be said of all these tumours that the cells constituting their parenchyma are of the same histological type as those of the parenchyma of the tissue or organ in which they have, or may reasonably be assumed to have, originated.

There are many tumours, the structure of whose cells differs radically from that of their parent tissue. They may conveniently be divided into three groups, although these overlap and merge into each other. The first group comprises the *teratomata*, whose parenchyma consists, in typical examples, of derivatives of the three germinal layers. The so-called *mixed tumours* constitute the second group. They are characterised by a double parenchyma, consisting partly of epithelium, which may be epi-, meso-, or hypoblastic, and in part of mesenchyme. The latter is usually represented by areolar and fibrous tissue, but occasionally contains heterotopic structures, such as bone, cartilage, etc. These two groups will be discussed in later studies. The present one is to be devoted to the third group. It comprises the *heterotopic tumours* (*sensu stricto*) whose parenchyma differs in its histological structure in part, at least, from that of the organs or parts of the body in which they are found. It will be convenient, for the reasons given in Study V., to limit ourselves to a full discussion of heterotopic epithelial tumours.

An epithelial tumour is heterotopic only when some or all

of its cells belong to a different histological type from that of the organ in which it has undergone its development. The best known examples are found in the squamous-celled carcinomata of mucous membranes lined by glandular epithelium, *e. g.* the uterus, the gall-bladder, etc. The change is one of essential structure and not merely of external form; intra-cellular fibrils, prickles and keratinisation are not characteristics of columnar epithelia.

1. *Pseudo-metaplasia, or formal accommodation.*—Before entering upon our subject, it is necessary to draw attention to certain changes often undergone by epithelial and endothelial cells, to which the name of "pseudo-metaplasia" has been given by Lubarsch,[41] and that of "formal accommodation" by Schridde.[67] They can be defined as "those alterations undergone by an epithelium which merely concern its external form, the functional structure characteristic of the tissue remaining unchanged" (Schridde,[67] p. 7). A classical example of this is the cubical shape assumed by the alveolar epithelium when the lung has been thrown out of action. It is a return to the less highly differentiated condition seen in the fœtus, and proves, as I have pointed out ([52], p. 81, footnote), that flatness is in this case a sign of physiological function, and that it requires a certain amount of effort for its maintenance.

This statement is equally true of the endothelium forming the lining to serous cavities and lymphatic spaces. It frequently assumes a columnar shape in inflammatory conditions, especially when it is covered by a fibrinous exudate. Lymphatics that are the seat of chronic inflammation and distension often contain papillomatous projections into their lumen, lined by large cubical and columnar endothelial cells.

Fig. 62 illustrates these changes in a tumour of lymphatics. It represents part of a subcutaneous cystic lymphangioma of the sacral region. Segments of two cystic lymph channels are present in the lower part of the drawing. They are lined by flat or cubical endothelial cells. Above them is seen a part of a collapsed space, which forms a crescentic cap to the lower right-hand cyst. Owing, no doubt, to the diminution of tension caused by its collapse, this space is lined by proliferated endothelium, many of whose cells are very tall and cylindrical. Branched papillæ have been produced, and the endothelium has budded into the neighbouring loose areolar tissue. These buds have become channelled, and have assumed shapes that closely simulate secreting glands. No structural alteration has taken place in the endothelium; its cells have only changed their external form.

The drawing indicates that a certain amount of rejuvenescence can take place in a tumour. As long as the cysts are distended with lymph their lining consists of flat, differentiated endothelial cells, that do not proliferate, except to the extent of keeping pace with a possible increase of circumference of the cavity. Once they have ruptured and collapsed, the diminished tension allows the endothelial cells to proliferate. They now increase in bulk and once more assume the functions, as well as the shape, of angioblasts, and give rise to a new growing point

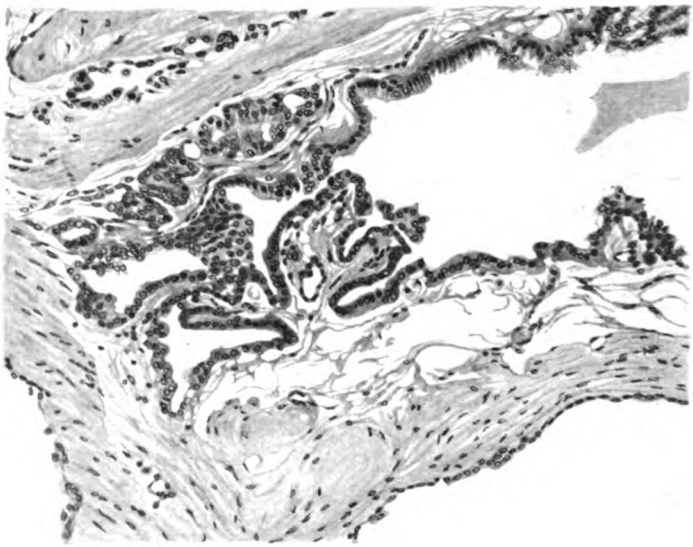

FIG. 62.

Cystic lymph-angioma of subcutaneous tissue. Magnif., 180.

for the tumour. Does not this observation support Child's [7] arguments that every actively proliferating tissue in the body actually becomes younger, and that a limited amount of rejuvenescence is constantly taking place?

Numerous other examples of the formal accommodation of the cells of tumours to alterations of environment could be given. The best known is perhaps the so-called *parenchyma* giant-cell, which is found in many rapidly growing carcinomata and sarcomata. These cells are distinguished by great diversity of size and shape, even in the same field of a section. They owe their origin to incomplete division, and possibly to confluence as well. Enormous hyperchromatic mitoses are frequent within them. They are probably the result of a disturbance of nutrition.

Their marked polymorphism proves that parenchyma giant-cells are not cells *sui generis*, but that they are purely secondary formations. It serves to distinguish them from *foreign-body* giant-cells, which are always found around insoluble substances, such as tubercle bacilli, cholesterin crystals, spicules of dead bone, ligatures, etc., as well as from *marrow* giant-cells and from those characteristic of the so-called *myeloid* tumours of bone, whose structure, although subject to slight individual variations, always conforms to a definite type.

Simple changes of external form are often spoken of as "metaplasia," even by pathologists of note. They have, of course, nothing to do with this change, which, as we shall see, is a profound one, leading to alterations of intimate structure.

2. *Prosoplasia.*—It is a significant fact that carcinomata, far from obeying the laws made in text-books for their guidance,* often produce the physiological secretion or metamorphosis of their tissue of origin in excess. This is especially true of squamous-celled carcinomata, and is their most constant feature. Practically every cutaneous epithelioma produces an enormous amount of keratin which, being formed from the oldest cells on the surface and near the centres of its broadest papillæ and processes, covers the surface or remains imprisoned beneath it, where it is compressed to form the characteristic horny nests or pearls.

These horny pearls are not found exclusively in epitheliomata, although they attain their greatest degree of development in them. They are frequently observed in inflammatory conditions associated with increased production and lengthening of papillæ. They are the result of a physiological process of hyper-keratinisation, which depends simply upon an increased production of cells. Its object, if one may speak of one, is, no doubt, to afford additional protection for the inflamed and damaged deeper tissues. This is attained when hyper-keratinisation affects the surface. When, however, it extends to the centres of the papillæ it becomes useless and ceases to be physiological. A beautiful illustration is given of the way in which, with an abnormal environment, such as a slight anomaly of position, a useful physiological process becomes a useless or even harmful pathological one. No better instance of the essential oneness of physiology and pathology could be found.

Keratinisation of a pronounced degree is often found in carcinomata of mucous membranes lined by non-keratinised squamous epithelium, *e. g.* in the tongue, œsophagus, cervix

* *Vide* Study I.

uteri, etc. But the production of horn is one of the potentialities of the cells of these organs, since it is of frequent occurrence in inflammations. One of the physiological properties of the tissue is merely accentuated in its new growths.

I [52] have drawn attention to the fact discovered by Schridde,[66] that the so-called "transitional" epithelium of the urinary passages is a squamous epithelium. Normally it persists in a lowly state of differentiation, but when irritated and inflamed, it often proceeds with its development, and gives rise to a typical epidermal epithelium with a *rete Malpighii*, prickle-cells, keratohyalin, and horn. This it does irrespective of its origin, since the cloacal (endodermal) lining of the bladder and

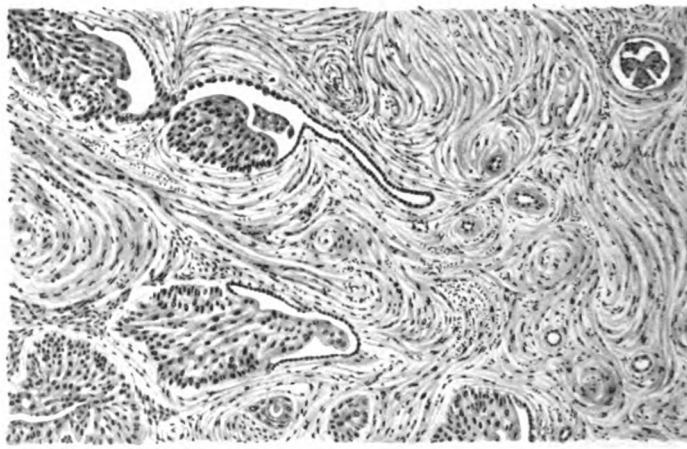

FIG. 63.

Cancroid of renal pelvis. Extension within tubules of kidney. Magnif., 90.

that of the Wolffian (mesodermal) trigone, ureters, pelves, and calyces tend equally to undergo this change. It is thus not surprising that intensely keratinised squamous-celled carcinomata are not uncommonly met with in all parts of the urinary passages. They are commonest in the renal pelvis, into which they project as villous horny masses. But they also freely infiltrate the substance of the kidney, and usually set up a great deal of fibrosis of its interstitial tissue without altering the shape of the organ, so that a kidney the seat of this type of new growth is exceedingly tough and fibrous. Fig. 63 represents the spread of such a tumour within the remains of renal tubules. The dense fibrosis is well shown, but a few tubules and glomeruli remain. The new growth consists of typical squamous epithelium, whose oldest cells are beginning

to keratinise. Large horny cell nests were found in other parts of the specimen.

It will be seen that all the cells of the tumour in Fig. 63 have assumed definite squamous characters. Even its youngest cells have the typical columnar shape of the germinal cells of the *rete Malpighii*. The differentiation in excess of the epithelium of the pelvis, or its prosoplasia, as it has been named by Schridde,[66] has affected first its germinal cells, which have produced exclusively descendants of the usual squamous type. This is how prosoplastic differentiation always proceeds in inflammatory conditions and as a rule in new growths. But

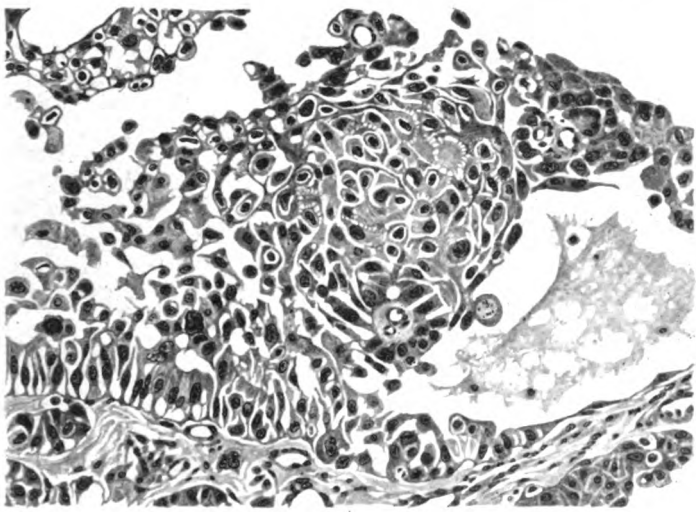

FIG. 64.

Transitional-celled carcinoma of bladder, with prosoplasia into prickle-cells. Magnif., 180.

Fig. 64 demonstrates that in carcinomata, at all events, it can proceed in a different manner. The drawing represents part of a malignant villous tumour of the bladder, whose germinal cells have retained the characters of " transitional " epithelium. Every here and there nests of swollen pale cells are scattered about in the superficial parts of the villi. They contain intracellular fibrils and prickles, as well as attempts at keratinisation. Individual cells and groups of cells have here undergone hyperdifferentiation independently of the germinal cells from which they are descended. This is a good instance of the want of proper control that is found in many tumours, and which has given rise to the erroneous impression that they do not obey the laws that govern the growth of normal tissues.

We must now inquire if the prosoplastic changes originate in the cells of the tumour, or if the latter is preceded by prosoplasia of the epithelium of the organ. I propose to discuss very similar questions in the third part of this paper. Here I need only state that both possibilities are realised. Squamous carcinomata have been known to arise in a renal pelvis or bladder whose epithelium had undergone extensive epidermisation. Fig. 64 shows that the converse obtains as well.

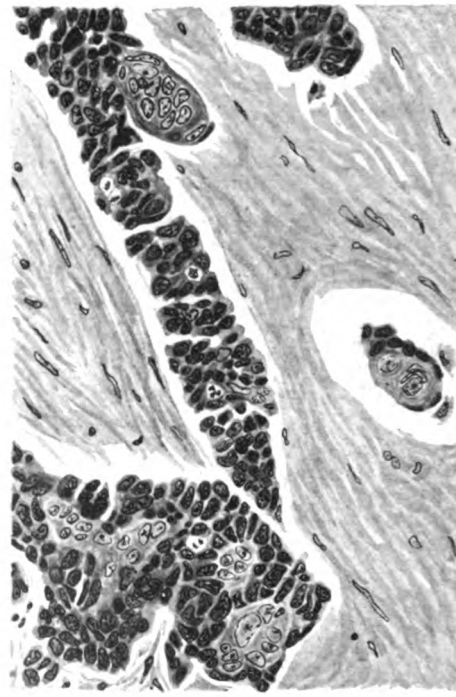

FIG. 65.

Basal-celled carcinoma of thymus. Differentiation into fibrillated, non-keratinised cell-pearls. Magnif., 350.

As both modes of formation actually occur, and since prosoplasia of a mucous membrane is succeeded by tumour formation in a percentage of cases only, it follows that the prosoplastic epitheliomata give no support to Cohnheim's theory. Prosoplasia of a mucous membrane is a physiological tendency of its epithelial cells, normally kept in check by their environment, by the functions they are called upon to perform. When the environment becomes abnormal the inhibition to fuller and more complete differentiation is removed, and development now proceeds upon physiological lines. There is no evidence

whatever that prosoplasia depends upon an abnormal predisposition of any sort, as has been suggested before now. Nor is there the slightest necessity to explain its presence by the help of purely hypothetical displaced epidermal cell-rests. It is true that at one time it was believed that the Wolffian duct is reinforced by cells of the ectoderm (Kollmann [36]), and that the tendency to epidermisation of the urinary passages was thought to give strong support to this view (Liebenow [40]). But since Schridde [66] has shown that their epithelium is squamous, a truer insight has been gained into its histology. We need no longer be surprised when meso- or endodermal squamous epithelium becomes keratinised, even though in normal circumstances it should persist in the simple condition of transitional epithelium.

Although keratinised squamous-celled carcinomata of the bladder, the ureters, and renal pelves strike us at first as something foreign to these organs, we must bear the fact in mind that they are after all composed of their own essential lining cells only. These tumours are therefore not heterotopic in any sense of the word, and must clearly be distinguished from those to be described in the third section of this paper.

This is the best place in which to describe a class of tumour rarely met with in the root of the neck, which, although its structure at first sight appears to be quite foreign to the part, in reality contains no heterotopic tissues whatever. Fig. 65 is a drawing of a microscopic slide of an extensive mediastinal tumour in a man of forty-six. It had affected all the lymphoid tissue within the thorax, and had extended into the lungs by way of the lymph-glands at their hilum. No other tumour was found outside the thorax. Its structure is that of a typical basal-celled squamous carcinoma, or "rodent ulcer," as it is still named by surgeons. I need waste no time in describing it. There can be no question that it arose in the thymus, which had merged and become incorporated in an enormous mass of new growth in the anterior mediastinum. I arrive at this conclusion partly by a process of exclusion, but chiefly because of the structural identity of my specimen with that of certain primary carcinomata of the thymus of which I have read. Schmidtmann,[63] who has collected the literature, describes two such cases. One of them consists chiefly of large cells, the other of small cells. She concludes, without giving her reasons, that the first of these originated in Hassall's corpuscles, and the second in the cells of the reticulum. Now Hammar,[21] who is undoubtedly the greatest authority upon the thymus, insists in a recent résumé of his work as well as

that of others, that Hassall's corpuscles are produced at all ages (from the third month of intra-uterine life to the seventieth year) from the cells of the reticulum. One or two of them increase in size, thereby pressing upon their neighbours and causing them to become flattened and to be grouped around them as a series of concentric laminæ, like the scales of an onion, and like the cell-pearls seen in squamous epithelia in every part of the body. He further points out that these corpuscles, or their smaller forms at any rate, in so far as they consist of nucleated living cells, seem to disappear again by a process of reduction in size of these cells, which reassume the characters of typical medullary reticulum cells. Mitoses are found in the reticulum cells even of the normal organ. The thymus, far from being a transitory organ, sensitively reflects, even in perfect health, all sorts of variations to an extent which is not exceeded by any other organ.

If we add the well-known facts that the thymus in man is developed from the endodermal epithelium of the third branchial pouch,* and that Hassall's corpuscles often contain kerato-hyalin and evidence of keratinisation, we can safely conclude that its reticulum is a form of squamous epithelium, whose cells in general are branched and aberrant in structure, but retain the potency to be differentiated into horny cell-pearls. They are, in this respect, analogous to the transitional epithelium of the urinary passages. The branched cells of the reticulum correspond in their functions with the basal germinal cells of squamous epithelium, since they alone divide.

If we accept Hammar's [21] views, the corpuscles of Hassall are not rudimentary structures, remnants of the pharyngo-branchial duct, but simply those cells of the thymus that have undergone the fullest amount of differentiation of which its epithelium is capable. They are the result of a process of physiological ageing of these cells, associated, it may be, with the performance of their functions. Hassall's corpuscles grow, not by division of their own cells, but by apposition of fresh reticulum cells. These, once they form part of a corpuscle, lose the power to proliferate. I therefore conclude that they are the last cells of the thymus that are likely to undergo blastomatous proliferation and to give rise to a neoplasm. Since neither the thymus as a whole, nor Hassall's corpuscles in particular, are rudimentary structures, it follows that the epithelial neoplasms of this organ give no support whatever to

* The lymphocytes or small thymus corpuscles are mesenchyme cells, that enter the organ from without and do not differ from those of lymphoid tissue in general (Hammar [21]).

Cohnheim's theory. The cells of the reticulum are basal germinal cells, and I can see no reason why it should not be these that give rise to neoplasms like the one under discussion.

One word more before leaving this subject. The small collections of large, fibrillated, non-keratinised squamous cells in Fig. 65 at first sight look very much like young Hassall's corpuscles. They may, indeed, represent these for all I know. But the tumour is a basal-celled carcinoma, one of whose most constant features is a certain amount of differentiation of some of its cells. This not infrequently proceeds to keratinisation and the production of horny cell-pearls, even in the most cellular of " rodent ulcers " of the face. It would, I think, be an exercise of the imagination to compare these structures with Hassall's corpuscles. I prefer to leave the question open, and not to use them to substantiate the thesis I upheld in Study I.

A basal-celled carcinoma of the epidermis is, after all, nothing more than an epithelial neoplasm, the majority of whose cells proliferate indefinitely after the manner and in the form of the germinal cells of the *rete Malpighii*, and in which differentiation is so slight as to be negligible. The only difference that I can see between it and a keratinising squamous carcinoma is that in the latter, coincidently with cell division, differentiation proceeds in the same manner, and very much at the same rate as in the skin. Now, all that we can say of all carcinomata of the skin is that they must arise in basal cells. The statements one frequently reads that " rodent ulcers " arise in hair-follicles, sebaceous or sweat-glands, according to the taste of the individual writer, appear to me to be flights of fancy, although I admit that they do occasionally simulate the outer layers of these structures very closely. But, then, these are all mere down-growths of the epidermis. I fail to see why a tumour of the epidermis that consists of and has arisen in the cells of its germinal layer—the mother-cells of all its appendages—should not mimic all the slight differences of form that these normally assume.

In conclusion: the view that the reticulum of the thymus is a form of squamous epithelium is borne out by two facts. The first of these is the manner in which Hassall's corpuscles are produced by the physiological differentiation of its cells. Again, additional support is given by the basal-celled carcinomata of this organ, several recorded specimens of which contained evidence of attempts at differentiation into fibrillated squamous epithelium. These tumours do not, in my opinion, originate in the corpuscles of Hassall, although the question if they do or do not is really quite immaterial to my argument,

since the corpuscles themselves are now known to be derived from the cells of the reticulum.

3. *Heterotopic Tumours.*—I must preface the following remarks with the statement that my paper upon "Heteromorphoses" [52] is, to a great extent, an introduction to them. I shall therefore take the arguments I developed in it for granted, and thereby save much needless repetition. I shall have occasion to discuss transitional, intermediate, or "indifferent" cells on the following pages, and wish it to be understood that I refer to structures similar to and comparable with those described upon p. 110, and illustrated in Fig. 16 of my former paper.

When the cases of formal accommodation and of prosoplasia in tumours have been excluded, there remains a considerable number of true heterotopic neoplasms, the physiological structure of whose cells differs radically from that of the epithelium of origin. Nearly all the new growths that constitute this group are squamous-celled carcinomata arising in mucous membranes lined by columnar epithelium. Columnar-celled carcinomata of squamous epithelium are extremely rare, but a few instances have been recorded. I propose, therefore, to discuss the former fully, and to describe the latter in as few words as possible afterwards.

There are very few parts of the body in which an innocent or malignant *heterotopic* tumour consisting wholly or in part of squamous epithelium has not been found.* These neoplasms vary greatly in frequency in different parts of the body. Squamous epithelium is found in about 50 per cent. of all carcinomata of the endometrium, whereas in some other organs its presence is almost unique or quite unknown.

Herxheimer [23] has proposed the name of "adeno-cancroid" for those malignant heterotopic tumours that contain areas of glandular carcinoma in addition to squamous epithelium, and that of "cancroid" for the pure squamous-celled carcinomata. Since these terms are most convenient, I shall adopt them.

Before describing the neoplasms I have seen which contain heterotopic squamous epithelium, it will be well to give a résumé of the most important of those I have met with in the literature.†

I will begin with the tumours of epiblastic organs. In the *mammary glands* there appear to be few records of malignant

* I repeat that I am not now discussing teratomata, dermoids, epidermoids, etc.

† My reading, although almost entirely limited to morphological subjects, has embraced as many of these as possible. It has therefore no pretensions to completeness in any one, and there are many papers that I have missed.

heterotopic neoplasms, although squamous carcinomata of the nipple are not very rare. Calderara,[5] however, has described two cases. The first of these was a large superficial tumour, not connected with the skin, which was perfectly normal and separated from it everywhere by a layer of fibrous tissue. The structure of the neoplasm was that of an adeno-cancroid. Numerous transitions were present between the glandular and the squamous-celled carcinoma. The latter was represented by large alveoli, lined by a layer of cylindrical basal cells, and occupied by horny cell-pearls. The second tumour, which measured 10 by 3 cm. in diameter, was situated deeply within the substance of the breast. It was lobulated and consisted of solid alveoli, that anastomosed with each other. The epithelial cells were largest near the centres of the alveoli. Here they had assumed the character of squamous epithelium with extensive keratinisation, often in the form of cell-pearls. The remains of the mammary ducts appeared to be normal. This case is a pure cancroid.—Several fibro-adenomata containing squamous epithelium have been described. Kuersteiner [38] saw a large one in a woman of forty-six, the spaces of which were lined by glandular, and by keratinising squamous epithelium. Cysts had been produced by the accumulation of the horny débris.—Grohé [20] found that the cavities of two cystic fibro-adenomata were partly or completely lined by fully differentiated squamous epithelium. Abrupt or gradual transitions were present between it and the neighbouring glandular cells. Tubules lined by the latter arose from the deep surface of the former. These facts led him to assume a true metaplasia.—Wilms,[76] on the other hand, explains these tumours on the lines of Cohnheim's theory, which was only to be expected of him. They do not arise in fully developed mammary tissue, but in cell-rests of ectoderm and mesenchyme, or possibly of ectoderm alone, since the mesenchyme is in part developed from this layer.—It is interesting to note that Fischer [14] injected an ethereal solution of Scharlach R into the mammary glands of rabbits. In one of his experiments the secreting acini, which retained their normal shapes, were, at the end of ten days, occupied by keratinised squamous epithelium. He believes this change to be a regeneration and atypical differentiation of the epithelium of the ducts, following the destruction of that of the acini.

I have not looked up the literature of heterotopic carcinomata of the nose or the air-sinuses.

Within the *cranial cavity* squamous epithelium is found in three situations. (1) In the *meninges*. Here it forms a lining for the cholesteatomata, whose classification we owe to Bostroem.[2] These are dermoid and epidermoid cysts,* and are outside the scope of the present paper. (2) Within the *anterior lobe of the*

* They are not true tumours or blastomata, but malformations, as I hope to point out in a future study. They have, however, been known to become carcinomatous (Rossknecht [56]).

pituitary, where a number of squamous-celled carcinomata have been described, since their true nature was first appreciated by Erdheim.[12] They are characterised by the presence of intracellular fibrils, prickle-cells, and a marked tendency to necrosis and calcification, with replacement of the dead calcified tissue by bone. Keratinisation is usually absent, but was first seen by Strada.[71] * (3) In tumours of the epithelial lining of the *ependyma* and *choroid plexus* of the ventricles. The first of these was, I believe, described by Selke [68] in a woman of forty-two. It arose in the third ventricle, in connection with its ependyma. Its covering consisted of squamous epithelium resembling the epidermis. Keratinisation was absent, although cell-pearls, consisting of nucleated cells, were observed. The epithelium of the surrounding ependyma was identical in structure with that of the tumour. An irregular branched tubule, lined by squamous epithelium, was present within the neighbouring nervous tissue; it was not connected with the tumour or the ependyma. The pituitary was normal. Selke believed his case to be the result of a local malformation, such as a displacement of epidermis of the oral cavity.—The next is the specimen described by Mott and Barratt [45] as a cystic tumour (epidermoid) of the third ventricle of a man of twenty-eight. The ventricular lining was thick and opaque, with numerous small cauliflower-like excrescences, chiefly below, and towards the aqueduct of Sylvius; the largest of these was nearly 1 cm. high. Under the microscope they were found to be papillomata, consisting of compound club-shaped processes of loose, œdematous connective tissue, covered by squamous epithelium bearing a very close resemblance to the *rete Malpighii* of the skin, its basal cells being small and columnar, and the others polyhedral, with a tendency to become flattened near the surface. The polyhedral cells exhibit prickles and frequently dilatation of the prickle-spaces. No mention is made of keratinisation. Fig 6, a low-power drawing of two papillomata, shows that the ependyma lining the ventricle between them consists chiefly of a single layer of cubical or columnar epithelial cells, except around the base of the upper one, where it is squamous. Mott and Barratt believe the tumour to be an epidermoid, that has arisen in displaced epiblastic cells, intended to form skin. These were carried into the third ventricle by the blood vessels at the time of the invagination of its roof to form the epithelial lining of the choroid plexus. They regret that the pituitary should not have been examined, since its origin from a diverticulum of the nasal mucous membrane might explain the displaced epidermal cells.—Herzog [25] described a large cyst of the inferior vermis of the cerebellum of a child of six. It was not connected with the fourth ventricle, and was lined by squamous epithelium, whose superficial cells were keratinised. The chemical reactions of this horny

* These tumours correspond very closely in their structure and behaviour with the calcified epitheliomata of the skin, one of which I have described.[70]

substance were almost, although not quite, identical with those of epidermal keratin. The cyst is not a dermoid, but an ependymal cyst, or a diverticulum of the fourth ventricle, whose connection with it was obliterated. It represents the diverticulum around which the cerebellum of the chick is developed,* and which is not normally present in mammalian embryos. The cells of the medullary plate are identical with those of the epidermis before the closure of the neural tube. Differentiation of both kinds of cell does not take place until later. The whole of the neuroglia is ultimately derived from the ependyma. Neuroglia fibres represent a process of physiological ageing of its cells analogous, although not identical with keratinisation of epidermal cells. The squamous lining of the cyst is the result of " atavistic " metaplasia of the epithelium, of a return to an onto- and phylogenetically less differentiated cell type.—I must here mention Boudet and Clunet's [3] first case. It is a papillary and cystic infiltrating tumour of the right cerebral hemisphere of a man of forty-five. It was directly connected with the choroid plexus of the lateral ventricle and projected into the latter. Its lining consisted of a single layer of cubical or columnar epithelial cells. There can be no question of its origin from the epithelium of the plexus. The fact that interests us here is this : the ependymal epithelium lining the ventricle had the structure of squamous epithelium, without intercellular prolongations, at several spots in the vicinity of the tumour.—Since it is not my object to investigate the histiogenesis of the intra-ventricular cholesteatomata, but to inquire if it be possible for the epithelial cells of the ependyma and choroid plexus to produce squamous epithelium, I will do no more than mention cases that are too far advanced to be of the same value as those I have abstracted. Those of Saxer [59] (Case 3) and of Ziegler [77] (solid squamous-celled tumours of the third ventricle with small cysts), Boudet and Clunet [3] (Case 2 : cystic squamous-celled tumour attached to base of third ventricle), Scholz [65] (cholesteatoma of third ventricle), and of Frick [17] (cholesteatoma of fourth ventricle) form an instructive series.† An unbiassed and sufficiently skilful writer could, I am convinced, argue with equal success that they have originated in displaced epidermal cells, squamous islands in the infundibular process of the pituitary ‡ (in the case of tumours of the third ventricle), or in the ependymal epithelium, if not in all of these.

Before leaving the central nervous system, I must mention that Meyer [44] has briefly described a cyst lined by squamous epithelium in the midst of a mass of neuroglia within an ovarian teratoma.

* This statement is Herzog's, not mine (*vide* [52], p. 90).

† Saxer's [58] teratoma of the third ventricle completes this ascending series. He very wisely does not attach any weight to his own tentative explanation of it.

‡ Saxer [59] describes on p. 339 squamous cell-pearls in the anterior wall of the infundibulum, for the first time, to the best of my knowledge. Erdheim [12] did not do so until two years later. See also [52].

We come next to the organs whose epithelium is of mesoblastic origin. The only heterotopic neoplasm (*sensu stricto*) of the male organs of generation that has, to the best of my knowledge, been described, is the cancroid of the *epididymis* recorded by Rowlands and myself.[57] It was removed from a man of forty-six, who, however, died within two months of the operation, apparently from secondary deposits within the abdomen. No post-mortem examination was made. The neoplasm was a cancroid with prickle-cells, keratohyalin, and horny cell-pearls. The skin was not involved by it. We believed that, since the Wolffian duct is developed close to the epiblast, the assumption that the tumour had arisen in included epiblastic cells offers a true explanation of its histiogenesis.*

I know of only one tumour of the *ovary* in which squamous epithelium was found. It is a cystic adeno-cancroid, with cell-pearls, of the left organ of a woman of thirty-six, and was described somewhat too briefly by Hitschmann.[27] A year later the opposite organ was found to be similarly affected. It is possible that it may have been a secondary deposit of a uterine neoplasm.

The *uterus* is the organ of the body that is most frequently the seat of a heterotopic carcinoma. Gebhard [19] was one of the first to deal with this subject, and to describe two cases. The curettings of the first of these showed that the epithelium on the surface of the endometrium was replaced by downgrowths of non-keratinised squamous epithelium, with numerous mitoses. It was a cancroid of the surface epithelium. The second case was a typical cancroid with prickle-cells and horny pearls. The mucous membrane had disappeared, and was replaced everywhere by granulation tissue.—To Hitschmann [27] we owe one of the fullest accounts of these tumours, together with an analysis of their histiogenesis. He described seven adeno-cancroids and one cancroid of the endometrium arising in uterine glands. The conversion, or metaplasia, of their epithelium into that of the squamous variety is either diffuse and affects a whole gland, or circumscribed foci of squamous cells appear in the midst of the columnar epithelium. He also describes a case in which the whole of the mucous membrane of the cervix and body was lined by a very polymorphic squamous epithelium, with numerous mitoses and marked keratinisation, from which irregular prolongations, containing cell-pearls, pass downwards. Because of the atypical structure of the epithelium he regards it as a true surface carcinoma. He points out that metaplasia into typical non-blastomatous squamous epithelium does not occur in this organ, and suggests that it would be wise to drop terms like "psoriasis" of the endometrium. Hitschmann believes that meso- and endodermal mucous membranes share the potentiality to keratinise with those of ectodermal origin. Differentiation is the accentuation,

* It was I who made this statement, and I accept sole responsibility for it.

the preponderance of certain capabilities over others. The appearance of those that have not been entirely suppressed explains metaplasia. In conditions characterised by violent proliferation, such as in carcinomata, the faculty of the Müllerian epithelium of the embryo to give rise to both columnar and squamous epithelium is regained. Hitschmann most emphatically expresses his disbelief in the doctrine of the specificity of the germinal layers.—I shall have to refer later to the views of Herxheimer,[24] and have done so sufficiently in my former paper to those of Schridde,[66] who describe a cancroid and an adeno-cancroid of the endometrium respectively.

Embryonic tumours of the *kidneys* contain rarely small islands and pearls of squamous epithelium. Muus[47] has described such pearls, containing prickle-cells and granules of keratohyalin. They merge with the cells of the general epithelial parenchyma of the tumour. They are caused by metaplasia, since the transitions cannot be explained on the assumption that they arise in displaced cells of the ectoderm. —Wilms[76] describes keratinised nodules of squamous epithelium, with a *rete mucosum*, a *stratum granulosum* with keratohyalin, and a *stratum corneum*. These are characteristic ectodermal structures. The cell-rest in which the tumour originated must have been displaced at a very early stage of development. Ecto- and mesodermal cells may have been displaced together, or the displacement may have affected the ectoderm at a time when the mesoderm had not as yet been budded off from it, and it therefore still contained the characters of mesoderm, and the potency to differentiate into it.—Jenckel,[30] in a remarkable, large, non-malignant, tumour-like hamartoma of the left kidney of a woman of forty-three, found large cysts lined by squamous epithelium with palisade and prickle-cells, keratohyalin and horn. He regards them as derivatives of the ectoderm, displaced into the Wolffian duct, which have reached the kidney by way of the ureteric bud. He points out that the duct does not come into intimate relationship with the ectoderm until a comparatively late period of embryonic life, one subsequent to the differentiation of the mesoderm into myotome and nephrotome. It is unnecessary to assume a very early error of development to account for embryonic tumours of the kidneys.—Hedrén,[22] in a boy of eight months, found small, concentrically laminated horny masses, usually surrounded by one or more layers of small cubical cells. No prickle-cells or keratohyalin were present. He saw a few of these structures within dilated tubules, whose lining was identical with that of the others. It is obvious that the epithelial cells of the tubule proliferate at one spot into its lumen, and that they then undergo these changes. These are most simply explained as a metaplasia of the mesodermal epithelium of the tumour.

I will begin the enumeration of the heterotopic tumours of the entodermal organs with those of the *thyroid*. Squamous-celled carcinomata of this gland are rare. Hudson[28] described

an interesting example, which was removed by operation from a woman of forty-nine. "Microscopic sections * exhibit a portion of a colloid adenoma with part of its capsule, which is of excessive thickness and contains compressed thyroid tissue. Extending towards, and to some extent invading, this dense fibrous structure are elongated processes of squamous-celled carcinoma, many of which have a central lumen filled with cellular débris. None of the cells of the new growths show evidence of keratinisation, and no cell-nests are seen." Hudson very rightly argues that it is not a secondary deposit, and "that the manner of incorporation of the tumour in the thyroid gland, and the complete absence of lymphoid tissue, would seem to exclude the possibility of its having originated in a secondary lymphatic gland infection. Mr. Shattock is of opinion that it had its origin in the epithelium of the thyro-glossal duct, the manner of its incorporation in the gland rendering such a mode of origin more probable than one from included elements of a branchial cleft."—Schmidtmann [63] has recorded a squamous-celled carcinoma of the left lobe of the thyroid of a boy of ten, with metastases in the cervical lymphatic glands. Its cells were fibrillated, but there were no signs of keratinisation. She inclines to the belief that the tumour originated in the epithelium of the branchial pouches.

A few heterotopic tumours of the *stomach* have been described. In Pollack's [54] case the primary growth was a pure columnar-celled carcinoma, whereas the pulmonary metastases had the structure of adeno-cancroids, and contained nests of squamous epithelium, with inter-cellular fibrils and early keratinisation. Pollack concludes that the neoplasm cannot have originated in a cell-rest, since there is no squamous epithelium in the primary tumour,† and all its cells and those of the metastases are descended from others which have nothing to do with squamous epithelium in so far as their developmental history is concerned. Because of alterations in the external conditions, the columnar cells of the secondary deposits have undergone a metaplasia into squamous epithelium.—Lubarsch [42] did not discover the true nature of a neoplasm of the pylorus until after he had examined its metastases in lymph-glands. These contained areas of squamous epithelium in addition to a columnar-celled carcinoma. Upon re-examination of the primary tumour he found a small amount of this tissue in addition to the columnar epithelium of which it consisted, and thus established the diagnosis of adeno-cancroid.—Herxheimer [23] has recorded an adeno-cancroid of the pylorus that had produced no secondary deposits. He was able to demonstrate the presence of protoplasmic fibrils, prickles, and of keratinised cell-pearls, as well as numerous transitions between the squamous and the tubular parts of the neoplasm. The latter greatly preponderated. He is unable

* But not the illustration, which is a photograph of a kind with which I am but too familiar.

† It does not appear from the description that complete serial sections of the tumour were examined.

definitely to exclude a metaplasia of the columnar cells of the tumour, or the presence of a displaced cell-rest of œsophageal epithelium. The simplest and most likely explanation, however, seems to him to be given by the assumption that certain cells of the pyloric mucous membrane had persisted at a stage of development at which they were able subsequently to undergo differentiation into squamous and into columnar epithelium.—Calderara's [5] case is a typical cancroid of the pylorus, with keratinised cell-pearls.

Heterotopic neoplasms of the *intestines* are as rare as those of the stomach. Bohm [1] described a case of extensive epidermisation of the distal six or eight cm. of the rectum, with a large, ulcerated, squamous-celled carcinoma immediately above the anus. The patient, a woman of forty-seven, had suffered for fourteen years from ulceration of this part of the gut, the result of a tear during parturition. He ascribes the epidermisation to direct extension of the anal epidermis. The cancroid has originated in it.—Herxheimer [23] gives a description of the histological appearance of a colloid columnar-celled carcinoma of the cæcum, scattered about in all parts of which there are islands of squamous epithelium, with protoplasmic fibrils, prickles, and signs of keratinisation. He was unable to demonstrate transitions between the two kinds of epithelium.—Muenter [46] records briefly a cancroid of the vermiform appendix, and a malignant adenoma of the rectum, whose surface was covered by squamous epithelium.—Schmidtmann [63] found a pure cancroid of the ileo-cæcal valve in a man of sixty-five. It had attained large dimensions, and had given rise to secondary deposits in the lymph-glands. It contained many keratinised cell-pearls. The mucous membrane of the cæcum, even where it covered the tumour, had retained its physiological glandular character. She concludes that, since there is no evidence in favour of a displaced ectodermal cell-rest in this part of the body, the tumour is to be explained as a result of metaplasia, especially since it was found at a spot where stagnation and irritation are liable to occur.

Heterotopic tumours of the *pancreas* are no commoner than those of the intestine, of which it is a diverticulum. The first case upon record is the cancroid of the head of the organ demonstrated by Israel.[29] The patient, a woman of fifty, had a columnar-celled carcinoma of the gall-bladder as well.—Lewisohn [39] described an adeno-cancroid of the head of the pancreas in a man of sixty-seven. Gradual transitions were found between the glandular and squamous parts of the tumour. The latter greatly preponderated. Its cells were fibrillated, and many intensely keratinised cell-pearls were present. The metastases in the liver and the regional lymph-glands consisted of pure squamous-celled carcinoma. Lewisohn, a pupil of Weigert, explains the histiogenesis of this neoplasm on the katabiosis theory of the latter, as a metaplasia of endodermal columnar epithelium into ectodermal squamous epithelium. More correctly, real ectodermal epithelium is only simulated,

because the katabiotic processes, undergone by certain ectodermal cells during their ageing, are here only produced artificially, so to speak. The cause of the metamorphosis is unknown.*—Herxheimer [23] found an adeno-cancroid of the body and tail of the pancreas in a woman of sixty-five, with metastases in the regional glands and the liver. The histological structure of the greater part of the tumour is that of a basal-celled carcinoma, with scanty scattered areas of differentiation into prickle-cells and horny cell-pearls. The columnar-celled part is limited to the tail of the organ. He was unable to find transitions between the two types of new growth. No mention is made of the structure of the metastases, except that the minute deposits in lymph-glands were composed entirely of basal-celled carcinoma.

In marked contrast to the rarity with which heterotopic tumours have been found in the gastro-intestinal tract and the pancreas is their relative frequency in the *gall-bladder*. I need not again go into the literature, since I did so fully some years ago,[49] in a paper in which I collected references to sixteen cases and described three new ones. All of these were pure cancroids, with the exception of two. These contained areas of columnar-celled carcinoma as well. Prickle-cells, or keratinised cell-pearls, or both were found in all the specimens. There is, however, one point that appears to me to be of sufficient importance to be reiterated here. Whereas squamous epithelium has never yet been seen in the mucous membrane of a normal gall-bladder, and once only in an organ that was inflamed and contained no new growth (Lubarsch [41]), it formed a lining to a part, at least, of its cavity in six of the cases associated with carcinoma (Ohloff,[53] Weber,[74] Rhein,[55] Nehrkorn,[48] Deetz,[9] Speese [70]).

Herxheimer [24] mentions the fact that he has seen two additional cancroids of the gall-bladder. His cancroid of the *common bile-duct*, and the adeno-cancroid figured by Kettle [34] (Fig. 54) are the only two heterotopic tumours of this viscus that I know of.

Hippel [26] has described a remarkable tumour of the *liver* of a child twenty-one months of age. It had the structure of an adenoma of liver cells, with scattered horny cell-pearls. They were surrounded by small cells whose morphological structure was indefinite. These took on the form of squamous epithelium on the one hand, and passed gradually into hepatic cells on the other. Hippel explains his case as a congenital mixed tumour, that has originated in hepatic cells owing to some developmental disturbance. Since it contained islands of cellular hyaline cartilage as well, he concludes that proliferation with de-differentiation of the epithelium and of the connective tissue of the malformation is responsible for the production of the neoplasm.

* Lewisohn's arguments are couched in very obscure language. I do not understand a single word of them.

When we come to examine the *respiratory tract*, we find that nearly all the epithelial tumours of the *larynx* and the *trachea*, the benign papillomata as well as the most malignant carcinomata, consist of squamous epithelium, and that glandular and columnar-celled neoplasms are very rare in these situations. This fact becomes all the more remarkable when we remember that the greater part of both larynx and trachea is lined by ciliated respiratory epithelium. The only areas that possess a squamous covering in the normal individual are the edges of the superior orifice and the back of the epiglottis, the true vocal cords, and scattered patches found here and there above the glottis (Schaefer,[60] p. 576).—Schridde [66] (p. 66) states that he has seen small islands of squamous epithelium on the membranous part of the trachea on two occasions. Carcinomata of the bronchi, however, although by no means common, are, I believe I am correct in saying, more frequently columnar than squamous-celled.—Siegert [69] has described a branched papilloma of the bifurcation of the trachea in a man of fifty-four. Its surface was covered by squamous epithelium, with prickle-cells and keratinised pearls, whose line of union with the respiratory epithelium of the mucous membrane at its base was perfectly abrupt. He points out that the bifurcation corresponds with the spot where the respiratory tract is first separated from the fore-gut. The presence of the tumour is to be explained by the persistence of an embryonic rest with epidermoidal characters at this point.*—Ernst [13] gives a careful account of a papillary cancroid of the bronchus of the right upper lobe of the lung of a man of fifty. It had given rise to metastases in the bronchial glands, the dura mater, the brain, and the left suprarenal. He was able to demonstrate the presence of cylindrical basal cells,

* It will be convenient for me to discuss Siegert's hypothesis here. I do not for one moment deny that his papilloma can be explained very well as an anomaly of bulk or of blending (*vide* Study II.) at the time of the first appearance of the pulmonary diverticulum of the fore-gut in the 3 mm. embryo, at the end of the third week (Broman,[4] p. 305). At this time the fore-gut is lined by a single layer of cubical epithelium. Ciliated cells first make their appearance in the œsophagus in embryos of 44 mm. (ten to eleven weeks), and squamous cells in those of 100–105 mm. (seventeen weeks) (Schridde [66]). Should cells destined to give rise to œsophageal epithelium have been displaced in a 3 mm. embryo, they would presumably undergo their normal differentiation into ciliated epithelium during the tenth week. It is difficult to explain why they should not persist in this form indefinitely in the congenial company of the surrounding ciliated respiratory cells. If it be granted that the locality, as part of the environment, influences the direction that differentiation takes, we should, in fact, expect them to remain ciliated throughout. We shall see on another page that the epithelium of all parts of the respiratory mucous membranes readily reacts to chronic irritation by becoming changed, or by undergoing a metaplasia into squamous epithelium. It is therefore far more reasonable to suppose that the epithelium of Siegert's papilloma underwent this change in response to an alteration of its environment, than to postulate an origin in an hypothetical cell-rest. Indeed, I assert that the cells of such a rest could only have become squamous in response to some external stimulus (such as the mild degree of irritation produced by proliferation of the mesenchyme of the papilloma), and not because it was ordained from the beginning of time that they should do so. This argument applies with equal force to the cells of the trachea themselves.

a *rete Malpighii*, a layer of prickle-cells, keratohyalin and horn, and numerous cell-pearls. Keratinisation was very slight in the secondary deposits.—Watsuji,[73] in describing four cancroids of the lungs, was able to show that the tumour was, in each case, in direct communication with a bronchus. The mucous membrane of the latter was converted into squamous epithelium, with prickle-cells and keratinisation. He is convinced that these neoplasms never originate in the alveolar epithelium. They always arise in that of a bronchus, which has undergone metaplasia as a result of chronic inflammation, which is generally tuberculous.—Schridde [66] informs us briefly that he has seen eight cancroids of the lung, none of which had undergone keratinisation. More or less extensive areas of glandular carcinoma were not very rarely present in them. In one case he found these tubular formations in the metastases in the kidneys and the liver, whereas the primary tumour was a pure cancroid.—Kawamura [32] described an adeno-cancroid of the bronchus. No intermediate stages between the columnar and the squamous cells were made out. The tumour originated in a bronchus, whose epithelium had returned to a stage of incomplete differentiation, and had then re-differentiated in both directions. The columnar cells of the carcinoma then overran the squamous ones.

Several heterotopic cancroids of the *prostate* have been described. Schmidt's [62] case in a man of fifty-three is of interest. The organ was found to be enlarged, and to contain within its tubules masses of loose squamous epithelium, resembling that described by Schlachta [61] in the last weeks of fœtal life. The accessory prostatic tubules of the urethra were hypertrophied. Their epithelium showed signs of intense proliferation, and was typically squamous in structure, with prickle-cells, keratohyalin, and horn. So intense was the proliferation, that Schmidt believes it to be blastomatous. He is inclined to regard the case as an early prostatic carcinoma.—Lubarsch [42] mentions two cancroids and one adeno-cancroid of the prostate.—Schridde [66] has seen typical squamous epithelium restricted to one part of an adeno-carcinoma of this organ.—Kettle [35] described an adeno-cancroid of the prostate of a man of sixty-two, with metastases in the regional glands and the liver. Prickle-cells are not well formed, but keratinisation is often very extensive. Transitions between the two types of cell are present. In addition, the conversion of the cells of the squamous epithelium into sarcomatous tissue, *i. e.* mesenchyme, is noted. The metastases in the liver contain both glandular and squamous epithelium.

I now propose, as briefly as possible, to review the heterotopic tumours that I have seen, and to select certain cases for a more detailed description.

I will again begin with the *mammary glands*. The question arises: in which part of these organs do carcinomata originate?

Is it in the epithelium of the ducts, or in that of the secreting acini, if we leave the possibility of the presence of hypothetical cell-rests out of the question for the moment? For *a priori* reasons we should expect the less highly differentiated epithelium of the ducts to proliferate and give rise to tumour formation more readily than that of secreting acini.* That this is actually the case has very clearly and convincingly been demonstrated by Cheatle.[6] His great merit lies, in my opinion, in the fact that he has shown that all stages of tumour formation, from simple hyperplasia to malignant infiltration, are often present in the same specimen, and that the "primary cancer process" commonly affects extensive surfaces of the ducts.† By having shown this he has made his papers of primary pathological, as well as surgical importance. For he has reduced the hypothesis of the intervention of "cell-rests" to an absurdity, unless we are prepared to grant that all the epithelial cells lining extensive segments, or even whole ducts, in many different parts of a breast, are of the nature of congenital malformations or "cell-rests." We can therefore dismiss them.

I believe with Cheatle [6] that all, or nearly all carcinomata of the breast arise in the epithelium of the ducts, even when, as is sometimes the case, this cannot be proved from the histological structure of the tumour. But there is a certain type of carcinoma mammæ which for years has been believed to be of duct origin. It is distinguished by the presence of large rounded spaces, occupied by big, faintly stained epithelial cells, closely packed together, often surrounding a central lumen, filled with cellular débris and fatty secretion. In order not to multiply illustrations unnecessarily, I draw attention to Figs. 197 and 205 of Ewing's *Neoplastic Diseases* (1st Ed.). They are both typical instances of "duct cancer."

This type of carcinoma is very common in the breast. It is, perhaps, the commonest of all. I sometimes see three or four in a week. Fig. 66 illustrates a tumour of this kind. It was situated within the substance of the breast of a woman of thirty-seven, and was not attached to the skin. Since it presented no unusual features, either clinically or upon examination, the specimen was not kept, except for two pieces removed for histological diagnosis. These (Fig. 66) consist of a carcinoma, whose cells are arranged in the form of large alveoli with central lumina characteristic of these duct cancers.

* *Vide* Study II. p. 200.

† By Sir G. Lenthal Cheatle's kindness, I have had several opportunities of studying his beautiful preparations.

Branched acini are present as well. Instead of being polygonal and of presenting the usual structure of this type of carcinoma, all the cells are, in this case, squamous. When a suitable magnification is employed, intra-protoplasmic fibrils and prickles are to be seen nearly everywhere. Keratin and para-keratin are present near the centres of the alveoli, whose lumina are often filled with flakes of horn, mixed with the usual inspissated caseous secretion. A few horny cell-pearls are also present. The group of small, branched columns of cells in the figure is obviously the remains of a secreting mammary acinus. Its branches are filled with squamous epithelium, which has

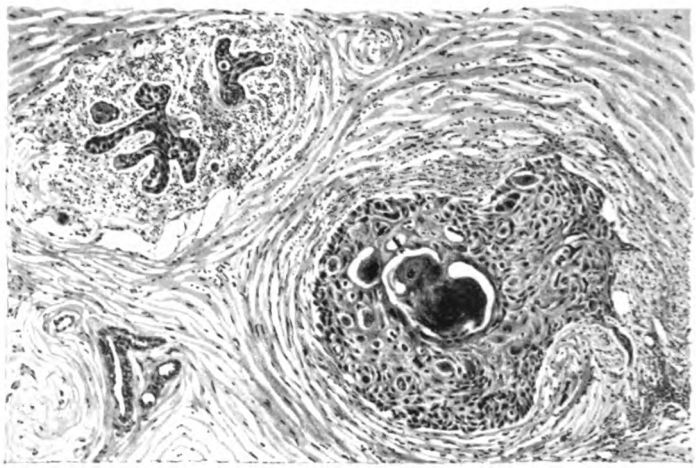

FIG. 66.

Duct carcinoma of breast, lined by keratinised squamous epithelium. Magnif., 90.

probably extended from a neighbouring duct-like alveolus, and has replaced the secreting epithelium. Since, unfortunately, the changes were far advanced in both the pieces examined, no definite opinion can be offered upon this point.

Here, then, we have a neoplasm, which has retained the typical architecture of a duct carcinoma, but whose cells are all of the squamous variety. Since it was fully established we have no indications of how these cells were produced. Nevertheless I believe that they have originated in those of the epithelial lining of a mammary duct.

I occasionally see a type of carcinoma mammæ which is superficial and which, by the time the case has come my way, has infiltrated the skin more or less extensively. These tumours are usually large and soft, and form a fairly well-defined mass

upon section. They generally consist of an alveolar or papillary part, composed of more or less columnar epithelium, and of a squamous part. The latter is always the more superficial of the two. Its cells tend to become more and more definitely squamous as the surface is approached. One of my specimens came from a woman of forty. Its central or deep parts consist of large irregular sheets of spheroidal cells, which at numerous points crystallise out, so to speak, into columns and tubules of columnar epithelium, that surround irregular cystic spaces, into which they project as highly complicated branched papillomatous formations. These areas have the typical structure of the "infiltrating duct papillomata" of the breast. Upon the other side the indifferent-looking spheroidal cells become larger and less "protoplasmic," and form the large alveoli, characteristic of the "duct carcinomata" described above. But in many of these alveoli the cells possess all the structural characters of squamous epithelium, to the extent even of having undergone keratinisation. Fig. 66 might easily have been drawn from this specimen, since it resembles its most squamous parts very closely indeed.

I must confess that I have paid very little attention to these tumours hitherto. Since all those I have seen were adherent to the skin, which was even ulcerated over them in some cases, I cannot exclude the possibility of the superficial squamous part, at least, having originated in the skin. But this supposition is very unlikely. In fact, I am not prepared to entertain it for one moment. It presupposes either the accidental presence of a cutaneous epithelioma immediately superficial to the mammary tumour in every case, or that one of these has "infected" the epithelium of the other organ. I have no use whatever for the "infection" theory of cancer in any form. Calderara's [5] first case, in which the skin was not involved, appears to be an earlier stage of this condition than those I happen to have seen. It seems to me that a far better explanation is given when we bear in mind Cheatle's [6] observations that extensive surfaces of the ducts are often involved in primary tumour formation. This involvement is not of the nature of an infection.* Put into a few words, it is the loss of control of the body over the mode and rate of growth of a large number of cells at the same time. I do not intend to amplify this statement here, as I shall have much to say upon the subject later.

I trust that I have made it clear that the cancroids and

* Unless my memory is sadly at fault, Cheatle himself made this quite clear in the discussion on his original paper at the Royal Society of Medicine in answer to a question.

adeno-cancroids of the breast I have been describing have originated in the epithelium of ducts; in epithelial cells, indeed, which, for all we know to the contrary, were perfectly normal functionating cells at some period of their life history.

The breast is a cutaneous gland formed by a process of budding or down-growth, like all the other epidermal appendages, from the epiblast. Since ontogenetically it is a part of the skin, it is surprising at first sight that it should give rise to cancroid formation as rarely as it does. But herein it does not differ from the other organs of the body. If I desired to lay down laws of oncology, I would begin with this one: the epithelial neoplasms of an organ or tissue do not depend upon its ontogeny, but upon its histology. It is immaterial where its cells have come from, which germinal layer they are derived from; all that matters is the direction their differentiation has taken. The typical carcinoma of a mucous membrane lined by squamous epithelium is a squamous carcinoma, be the mucous membrane the epiblastic skin or oral cavity, the mesoblastic cervix uteri, or the hypoblastic œsophagus. Again, the typical carcinoma of a secreting gland is a glandular carcinoma, be it the epiblastic mamma, the mesoblastic kidney, or the hypoblastic pancreas. The statements that are frequently made even to the present day, that freely keratinising carcinomata of the œsophagus or cervix have assumed "epidermal" characters are therefore contrary to experience, if not to reason. Even if we are prepared to accept the dogma of the specificity of the germinal layers, do we know its limitations? Cases like the sebaceous glands of the cervix uteri I [51] have described, are hard to explain on this doctrine and are well calculated to give us pause.

Since the breast is a secreting gland, its malignant epithelial neoplasms are typically glandular carcinomata. Our small digression has brought us to this question: How is it possible for the mammary epithelium to give rise to a cancroid, a tumour consisting of squamous epithelium? If we rule out embryonic undifferentiated cell-rests, a proceeding which I believe I have brought forward sufficient evidence to justify, in this as well as in earlier papers, we are left with two alternative explanations:

(1) Structural characters that were lost have been re-acquired by certain epithelial cells of the mammary ducts, a process that is spoken of as "metaplasia."

(2) Structural characters that were latent have become apparent. The cells of the ducts have merely exceeded their normal degree of differentiation. This phenomenon we designate by the term "prosoplasia."

I do not know which of these explanations is the true one, since, to the best of my knowledge, the histology of the epithelium of the mammary ducts has never been properly worked out, and its status established. It is possible that it may be shown to be an aberrant form of squamous epithelium, comparable with the "transitional" mucous membrane of the urinary passages, as demonstrated by Schridde,[66] and perhaps with the cells of the reticulum of the thymus. The fact that the adeno-cancroids described above become more and more squamous the nearer they get to the surface is suggestive. If we accept Cheatle's [6] statement, that large areas of the ducts are commonly involved in tumour formation, the histology of these neoplasms is readily explained, if it can be shown that the farther away we pass from the surface, the more recessive do the squamous characters of the epithelial cells of the ducts become. A good piece of research could be done to establish or refute this argument. Should it be established, the cancroids of the breast will cease to be true heterotopic tumours. They will then have to be placed with those resulting from prosoplasia.

I have never seen an *intra-cranial* heterotopic tumour of any kind.* Sir Frederick Mott has, however, had the kindness to show me the sections of his case (Mott and Barratt [45]). It will be remembered that he explains it as an epidermoid, whose epithelium is derived from the epidermis, some of whose cells had been accidentally displaced. Upon this assumption these were predestined to undergo differentiation in this direction, regardless of the exact part of the body in which it was undergone. I believe that two other explanations are possible, both of which presuppose that this epidermoid is a derivative of the neural epithelium.† They are contained in these words: "Metaplasia or heteroplasia."

It appears to me that the first question we must try to answer is this: Is this malformation (using the term in its widest sense) congenital, or can it have been acquired? If this question can be answered, we can proceed to inquire into the nature of the exact process that has caused it, if it be an

* I except those cancroids that have arisen within the air-sinuses and have perforated the bone. They will be discussed in the next paragraph.

† I use the word "epidermoid" advisedly in preference to "tumour," since it expresses nothing more than the fact that the cells have the structural characters of those of the epidermis. It does not necessarily convey the implication that these cells must be epidermal cells, although this is usually understood. Nor does the term imply that we are dealing with a true tumour, as I have already suggested in a footnote to this paper. All that it states is that cells of epidermal character are found in an abnormal situation, which they occupy as the result of an anomaly, which may be one of differentiation or of position or of blending (*vide* Study II. p. 199), and which may be congenital or acquired (*vide* Study IV.).

anomaly of differentiation or one of position. I confess that, before I had had the opportunity to examine Sir Frederick Mott's slides and to discuss them with him, I inclined to the belief that the epidermoid was acquired, and that a chronic inflammatory process had led to blocking of part of the third ventricle, to retention of cerebro-spinal fluid, and to a localised internal hydrocephalus. Localised proliferations of the ependyma had then taken place, and the proliferating epithelial cells had assumed the structural characters of squamous epithelium by a process of metaplasia. The reasons that led me to adopt this view were based upon Fig. 6 of Mott and Barratt's [45] paper. Here the papillomata are covered by squamous epithelium, which has extended for some little distance upon either side of them, whereas the intervening wall of the cavity is lined by columnar ependymal epithelium. I thus argued that the anomaly as a whole cannot possibly constitute one single epidermoid, but that each of the papillomata must have arisen in an independent displaced cell-rest. Now, all my observations that have been directed to the attempt to find the true significance of the rôle played by displaced cell-rests in tumour formation * have consistently shown me that the evidence is so slight as to be negligible, provided an alternative explanation be possible. I was, therefore, not prepared to accept the possibility of the presence and growth of several discrete displaced cell-rests in this case and, without knowing the specimen, rashly concluded that a metaplasia upon the basis of an acquired inflammation would explain it. Sir Frederick Mott, however, quickly showed me that I was wrong, by pointing out that the specimen shows no trace whatever of old inflammation. The only possible answer to our first question is, therefore: "A congenital anomaly."

This question having been disposed of, we can now inquire into the histiogenesis of this congenital malformation. The opposing explanations are here as elsewhere: displacement or heteroplasia. If we accept the former, we are bound to postulate several discrete epidermal cell-rests to account for the presence of multiple papillomata. If the latter, we must assume some anomaly within the neural plate or tube itself, which led to dilatation of that part of it which forms the third ventricle, to irritation of the epithelium lining it and to its proliferation, and to the abnormal differentiation of the proliferating cells in the alternative or recessive direction of those of other parts of the epiblast. I must leave the question here, since to give the reasons why I accept the latter view as the

* They were begun in 1909 (*vide* Study VI. p. 175, footnote).

more natural one would be to repeat most of what I have already stated at great length in these studies.

I may, however, be allowed a few remarks upon the ætiology of this anomaly, as opposed to its histiogenesis. Of this I know nothing. Even if we are prepared to accept a *vitium primæ formationis* of its cells, and to a far greater extent if we are not, we have still got to explain why and how several of those of the epidermis were displaced, a fact that explanations upon the lines of Cohnheim's theory consistently lose sight of. It is true that the alternative theory of heteroplasia labours under a similar disadvantage. There is, however, a difference which, although slight, is distinctly in its favour. On the hypothesis of displacement we must postulate an " error of development " at a very early period and of relatively enormous magnitude. On that of heteroplasia this was certainly not so great, since it may have occurred, and probably did occur, very much later, as late maybe as the time of the differentiation of the neural epithelium into ependyma.

These studies are not ætiological. I cannot, therefore, pursue the subject, except for a reference to what I have suggested upon pp. 197 to 199 of Study II. I am content if I have shown that heteroplasia, or the differentiation in the alternative prospective direction of the cells of the neural tube, can be taken into account in the explanation of the recorded instances of the presence of squamous epithelium within the ventricles of the brain.

I must, however, mention that Saxer [59] expressed a similar thought in these words: " In spite of the danger of being thought a heretic by many, I must most emphatically express the opinion that there is no possible objection to the view that epidermis-like structures can arise from the ependymal epithelium, *without* the presence of a congenital anomaly. The work of the past decades has shown conclusively, to my mind, that epithelial formations with all the characters of the epidermis can arise absolutely everywhere and from all epithelia, without any justification whatever for the assumption of a displacement of material from the epidermis."

Carcinomata of the *nose* and *naso-pharynx*, and of the accessory *air-sinuses* are far from common. When found, they can generally be shown to have originated in one of the sinuses, especially the maxillary antrum. Of the fourteen cases I have seen, three apparently arose in the nose itself, one in the naso-pharynx, and the others in the air-sinuses. Eight of these were antral growths. With but two exceptions, all these tumours are heterotopic, one is an adeno-cancroid, the

others are cancroids. These are usually of the basal celled variety, whose differentiation does not proceed beyond the formation of cells of the *stratum granulosum*. Keratinisation is, however, present in four cases. It is very feeble in the only tumour of the nose that exhibits it at all, but has led to the formation of many typical horny cell-pearls in three cancroids of the antrum.

The two tumours that do not contain definite heterotopic tissue are very different in their microscopic structure *inter se*. One is a tubular columnar-celled carcinoma of the ethmoidal sinuses of a woman of sixty,* which is unusually osteoplastic.

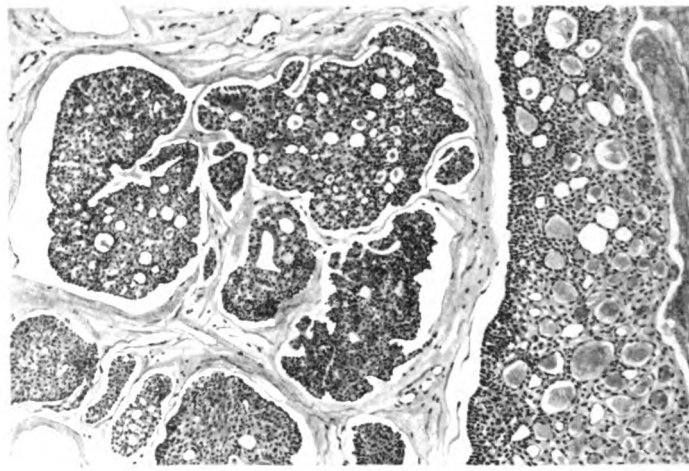

FIG. 67.

Cylindroma of maxillary antrum. Magnif., 90.

It is of interest to note that the respiratory epithelium upon some of the remnants of mucous membrane upon and around it has been partly replaced by non-keratinised squamous epithelium. The second of these tumours has the structure of a basal-celled carcinoma, the cells of which have, however, begun everywhere to undergo differentiation in the natural direction; irregular tubules, lined by cubical and columnar cells, being present in all parts of the sections. It was extirpated from the maxillary antrum of a woman of sixty-four.

My series of heterotopic tumours contains two cystic basal-celled carcinomata or cylindromata. One of these came from

* No fewer than eleven of my cases occurred in women. Chronic nasal trouble is notoriously commoner in the female than in the opposite sex. This suggests, although it does not prove, that this complaint is a predisposing cause of tumour formation of this part of the body.

the ethmoidal sinuses of a man of forty-three, the other from the maxillary antrum of a woman of fifty-nine. Fig. 67 represents one of the least cylindromatous areas of the latter specimen. I reproduce it here because I remember how puzzled I was some years ago to explain a similar, but more anaplastic tumour shown to me by Dr. Perdrau of the Lambeth Infirmary. It was attached to the petrous bone and projected into the temporo-sphenoidal fossa.

The last-mentioned specimen brings me to the two cancroids of the mastoid antrum I have seen. They are typical squamous-celled carcinomata with an amount of keratinisation that is unusual even in the skin. Parts of them consist entirely of large necrotic horny cell-pearls tightly wedged together. This tendency to hyper-keratinisation appears to be characteristic of this region, since it is occasionally occupied by a cholesteatoma, for whose origin in a displaced cell-rest there is no proof, in spite of the opinions often expressed.

All the heterotopic tumours discussed here have arisen in mucous membranes lined by columnar, ciliated, respiratory epithelium. They are all of them large and firmly established, and therefore quite unsuited for studies in histiogenesis. There is, however, one remarkable fact that throws much light upon the question of their origin. More or less extensive areas of squamous epithelium are to be found lining the inflamed or atrophic mucous membrane of every diseased nose, and of a good many normal organs as well. We owe much of our knowledge of this subject to Schoenemann.[64] He examined histologically the mucous membranes of all the turbinals of eighty-three consecutive post-mortem cases in adults, as well as of thirty newly-born infants. In only ten adults was he unable to demonstrate the presence of more or less extensive patches of squamous epithelium, whereas not one of the infants showed the smallest trace of them. He dismisses the possibility of congenital anomalies because of the latter fact, and concludes that the presence of squamous epithelium can only be accounted for by metaplasia, upon the basis of the proliferation resulting from chronic irritation and inflammation. I can fully confirm Schoenemann.[64] About 60 per cent. of my routine sections of mucous polypi and granulations of the nose, cut at haphazard, show the presence of squamous epithelium, often freely keratinised, and in acutely inflamed cases nearly always that of unmistakable transitions to the columnar epithelium as well. Schoenemann [64] states that he has never seen squamous epithelium within the air-sinuses. My knowledge of the literature is too defective to permit me to say if, or how often

it has been found since. I have, however, seen it in the ethmoidal sinuses of the case of columnar-celled carcinoma described above, as well as upon œdematous polypi of the same sinuses of a male of forty-five. Beautiful prickle-cells are present in the second case.

Since I am unable to prove the nature of the cells in which these cancroids have arisen, I can but express the opinion that they did so in the basal cells of the mucous membrane as they re-acquired, or soon after they had re-acquired, the prospective fate of being differentiated heterotopically into squamous epithelium. This change in their prospective fate occurred at a period of rapid proliferation, as in all other instances of metaplasia. It is impossible to say when they first assumed blastomatous characters, although it is probable that they did so at the same time.

The only heterotopic tumour (*sensu stricto*) of the *male generative organs* that I have seen is the keratinised cancroid of the epididymis I described together with Mr. Rowlands,[57] to which I have already alluded in an earlier part of this paper. I need hardly say that I have given up the idea long ago that it originated in displaced epidermal cells. Metaplasia into squamous epithelium is common enough in the tubules of the epididymis in chronic inflammations, especially in tuberculosis. There is thus no objection to the assumption that our cancroid is descended from the mesodermal cells of this organ.

I now turn to the female *organs of generation*, and begin with the ovaries. Only once have I seen squamous epithelium in a carcinoma of these organs. The case is represented by two large multilocular cysts, removed from the ovaries of a woman of forty-two. They possess the same histological structure, being composed of a fibro-cellular stroma, infiltrated throughout by masses of large irregular epithelial tubules, lined by cubical or columnar cells, and dilated every here and there to form large cysts, filled with the usual pseudo-mucinous secretion. These appearances are characteristic of a type of ovarian carcinoma which is common enough. The larger of the tumours * contains almost everywhere numerous areas of squamous epithelium inextricably mixed with the columnar cells. It possesses a well-marked germinal layer and typical prickle-cells. Cell-pearls can be seen in almost every squamous patch. Keratinisation is freely present, and numerous masses of dead horn, surrounded by large foreign-body giant-cells, occupy the stroma. These appearances are to be seen in Fig. 68. Where there is an

* I do not know the side it came from.

epithelial covering upon the surface of the tumour, it consists of a single layer of large, more or less distinctly fibrillated cells, whose outlines are often invisible, so that the appearance of a flat syncytium is produced. Local proliferations of these cells have taken place every here and there, the result being the production of a squamous epithelium, with elongated germinal cells, distinct prickles, and flattening of its superficial layers, in which keratinisation is absent (*vide* Fig. 68). In the smaller cystic tumour of the opposite ovary I have observed no squamous epithelium except upon the surface. This is generally covered

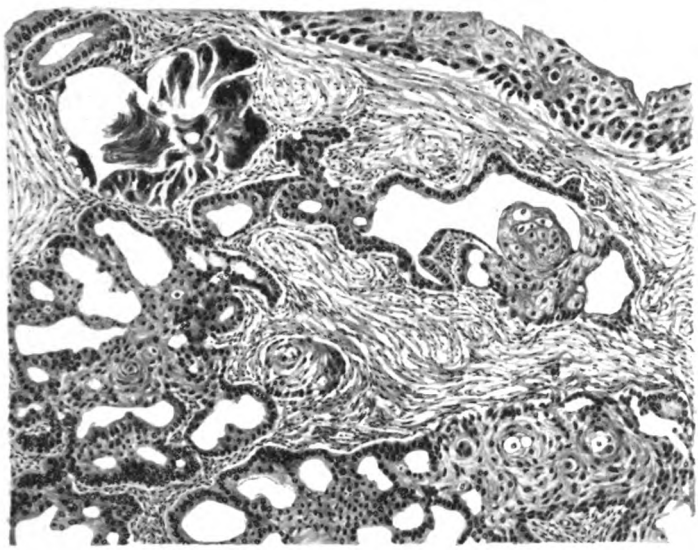

FIG. 68.

Cystic adeno-cancroid of ovary. Dead horn surrounded by foreign-body giant cells. Surface covered by squamous epithelium. Magnif., 100.

by a layer of columnar epithelium, from which tubular processes pass downwards to reinforce the general carcinomatous parenchyma. Every here and there the surface epithelium is replaced by masses of squamous cells, often surrounded at their edges by a zone of rounded or polyhedral deeply stained protoplasmic epithelium. Fig. 69 illustrates these appearances. They constitute the best instances of "transitions" I have observed in heterotopic tumours.

Of the thirty-six primary carcinomata of the body of the *uterus* I have seen, fourteen contain definite squamous epithelium. In five cases cells are present which, although they are probably squamous, are too indefinite to allow of certain con-

clusions. In the remaining seventeen cases I have seen no trace of the presence of this kind of epithelium.*

Six of the heterotopic tumours are cancroids, and eight adeno-cancroids. Of the former, one only is an extensively keratinised squamous carcinoma, indistinguishable from one of the skin. The others are of the basal-celled variety, with more or less successful attempts at differentiation into a *stratum granulosum* with prickle-cells, and into cell-pearls. The latter show signs of keratinisation or of the formation of para-keratin in three cases.

Of the eight adeno-cancroids, one has the architecture typical of columnar-celled carcinomata of the endometrium. It consists of branched tubules, lined by one or two layers of cubical

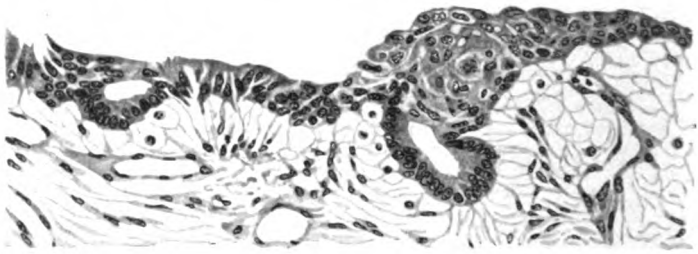

FIG. 69.

Tumour of opposite ovary. Surface lined by columnar and squamous epithelium. Magnif., 215.

and cylindrical cells. These are, however, interrupted at frequent intervals by islands of squamous epithelium, composed of fibrillated cells. They vary greatly in extent. The smallest consist of one or two squamous cells, the largest of many. They always abut on the connective tissue upon their outer side, so that the contour of the tubule is not interrupted. The larger islands project into the lumen of the tubule, since they consist of several layers of cells. Pearls are often to be seen, many of which are keratinised. The islands are always perfectly well defined, and there are no transitional cells at their edges. Another specimen presents the structure of a typical columnar-celled carcinoma in its deep parts. Towards the surface its tissues have, in response apparently to the irritation of a mild degree of sepsis, undergone extensive disorganisation. Many cells are necrotic, others have proliferated as rows and groups that have lost the epithelial habit of growth, and closely resemble a sarcoma or actively growing granulation tissue. Large

* My material consists merely of routine sections. I have carried out no systematic investigations.

keratinised cell-pearls have made their appearance among them. They are surrounded by a germinal layer of cells in every way indistinguishable from the others. These horny pearls are entirely confined to the superficial parts of the tumour. The remaining six cases are basal-celled carcinomata, with more or less successful attempts at differentiation into squamous epithelium on the one hand, and columnar epithelium on the other.

In the cases in which remnants of endometrium were found at the base of the neoplasm, these were always lined by columnar epithelium, and never contained squamous cells.

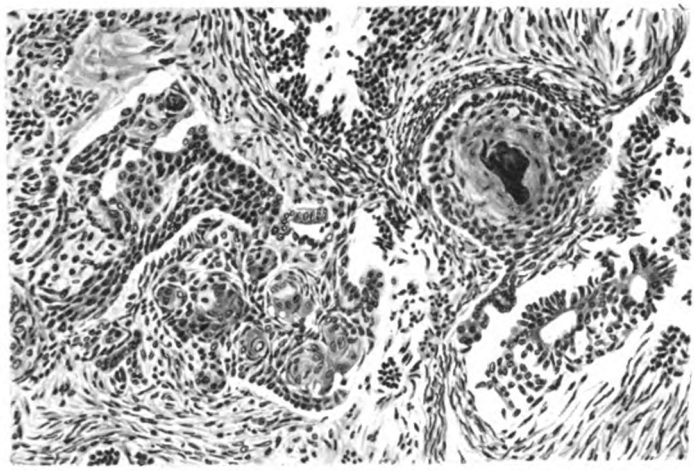

FIG. 70.

Embryonic tumour of kidney with keratinised squamous epithelium. Magnif., 190.

Since all these uterine tumours were fully established, every clue to the means by which the heterotopic tissue was produced had disappeared long before they were examined.

I have only seen one embryonic tumour of the *kidney*, in a girl of twelve, which contains squamous epithelium.* The greater part of the neoplasm is almost completely undifferentiated, and resembles a round and spindle-celled sarcoma. But differentiation has proceeded to a comparatively high state in many places, one of which is shown in Fig. 70. Long

* Cartilage and striated muscle cells and fibres are present. The former I have attempted to explain in Study III., upon another page of which I have tried to show that we do not possess data sufficient for an adequate explanation of the latter. Tumours of this kind appear to be of not infrequent occurrence on the Continent, if one can judge by the number recorded. They are certainly very rare here.

spindle-cells have been formed, most if not all of which are plain muscle fibres. Commencing tubule formation is also present. To the left of the drawing the germinal cells of the parenchyma are condensed. This area corresponds in appearance and in structure with the *rete Malpighii* of squamous epithelium, since its cells are fibrillated. An irregular *stratum granulosum*, with prickle-cells,* is present. Its cells are often swollen and form pearls, in some of which keratinisation has commenced. To the right of the drawing a large cell-nest can be seen, with a germinal layer, a *stratum granulosum, lucidum*, and *corneum*, the last of which is firmly calcified. These large keratinised cell-pearls are common, and many of them are much bigger than the one represented in the drawing. They are always very freely keratinised. It is perfectly clear from the sections and, I believe, from the figure too, that the squamous cells have arisen directly from those of the general germinal parenchyma of the tumour. At least, if a group of cells be looked at, all stages can be made out between young parenchyma cells and those that have acquired definite squamous characters. The latter are first condensed, and then acquire them. Conclusions more definite than these cannot, unfortunately, be drawn from fixed material. Their validity is, however, accepted in embryology, and must therefore hold good in tumours. In its manner of origin the squamous epithelium has taken the direct path, as in the case of Muus,[47] since it is differentiated directly from the germinal cells of the tumour. It will be remembered that in Hedrén's [22] case this took place from cells that had already acquired the characters of tubular epithelium. It is of interest to note the fact that both these modes of formation occur.

The next organ to be discussed is the *thyroid.* I have seen a freely keratinised squamous-celled carcinoma of the right lobe of this organ in a man of fifty-two. As he survived the operation, I cannot definitely exclude a primary growth elsewhere. There was no clinical evidence of one, and I have no doubt that this is a primary cancroid of the thyroid.

Fig. 71 represents part of a large cystic adenoma of the thyroid of a woman of thirty-two. The rest of the gland showed signs of nodular hyperplasia at the operation. The tumour is surrounded by a dense hyaline, partly calcified capsule. It is represented in the drawing, together with a few glandular alveoli, in and around which a good deal of desquamation, as well as of proliferation of epithelium and of connective

* The magnification employed was too low to show fibrillation or prickle-cells in the drawing.

tissue has taken place. Two alveolar spaces are partly filled with masses of squamous epithelium, and two cell-pearls are placed close to them, surrounded by hyaline stroma. A *rete Malpighii* and *stratum granulosum* with prickle-cells can readily be made out, and keratinisation, in the form of a small rounded mass of horn, has taken place within two of the squamous nests. A few small rounded or elongated processes of squamous epithelium are scattered about in the stroma. Similar structures were found in all parts of the capsule of the adenoma.

This case corresponds very closely with the one described by Hudson.[28] The latter was, however, a carcinoma, whereas

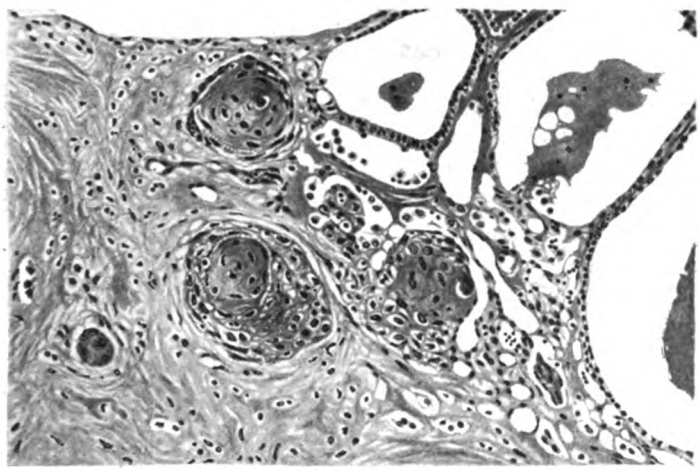

FIG. 71.

Squamous epithelium in capsule of cystic adenoma of thyroid. Magnif., 190.

no signs of malignancy are exhibited by my specimen. Since many of the collections of squamous cells are found within spaces occupied by thyroid epithelium, in and around which proliferation has taken place, I conclude that we are looking at an instance of metaplasia resulting from an inflammatory reaction. Because of this I can see no grounds for the belief that the squamous epithelium represents remnants of the thyroglossal duct, except in so far as this is true of the whole thyroid, nor does its distribution within the capsule of the adenoma, which is clearly a late stage of nodular hyperplasia, support this view.

I must here recall to mind the cystic adenoma of an accessory thyroid described in Study V. (Fig. 47), which contains numerous islands of non-keratinised squamous epithelium.

I have seen no heterotopic tumour of the alimentary canal, and but one of the *pancreas*. It was a large tough neoplasm of the head of the organ, with numerous secondary deposits in the lungs, in a woman of fifty-four. Its greater part has the structure of proliferated ducts, the arrangement of the epithelial cells being markedly tubular. At several points of its periphery, where it is infiltrating the sub-peritoneal tissues, isolated groups of solid acini, consisting of keratinised squamous epithelium, are present. Part of the largest of these is shown in Fig. 72. No transitions to the tubular carcinoma were seen, nor were acini found containing both kinds of epithelium. The pulmonary metastases consist entirely of tubular carcinoma, often with an

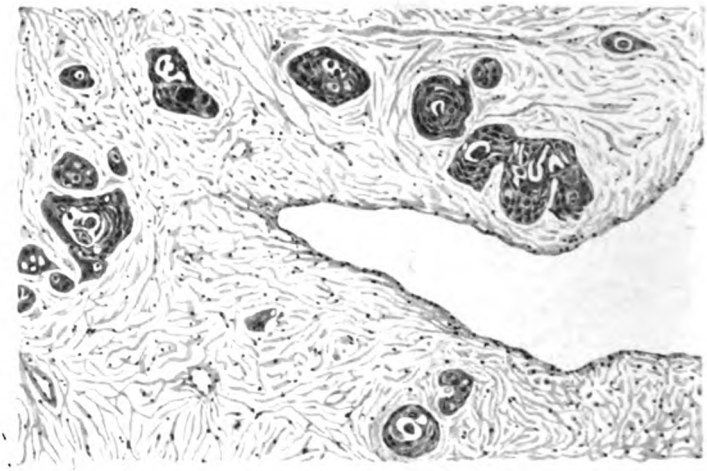

FIG. 72.

Squamous part of adeno-cancroid of pancreas. Magnif., 95.

excessive amount of mucoid degeneration of its cells. Remnants of pancreatic tissue are present in many parts of the primary tumour. The epithelium of their ducts and acini shows no anomalies.

In addition to the three cases recorded,[49] I have examined one adeno-cancroid of the *gall-bladder* in a woman of sixty-one. It is of considerable interest because of its unusual structure, which is represented in Fig. 73. The greater part of the pieces removed at the operation consists of a basal-celled carcinoma, shown in the upper part of the drawing, in which differentiation into a *stratum granulosum* with prickle-cells has taken place irregularly at numerous points. This process generally stops at this stage, and I have found only two small keratinised cell-pearls in the sections examined. Another change is apparent

at several points of one part of the tumour. Here differentiation of the basal cells has proceeded in the direction of columnar epithelium, whose cells are grouped around a wide lumen. Typical goblet-cells make their appearance. They form either a lining to a wide lumen, as in the upper right-hand corner of Fig. 73, or have produced branched glandular structures, shown in the lower part of the drawing. These formations are of the type of intestinal epithelium, and bear no resemblance to that of the gall-bladder or of those carcinomata of it that I have seen. This resemblance to intestinal epithelium becomes all the more striking when we remember that goblet-cells are uncommon in the gall-bladder. The glands which are freely

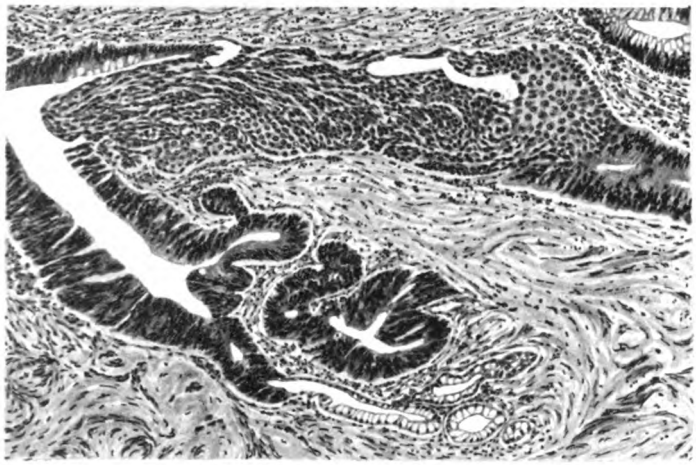

FIG. 73.

Adeno-cancroid of gall-bladder. Magnif., 125.

budded off from Luschka's tubules in this condition are lined by clear cells, resembling those of Brunner's glands, and not by goblet-cells. No remains of the mucous membrane of the gall-bladder were present in this case.

I have seen three cancroids of the *lung*, all of which obviously originated in a bronchus, in individuals from forty-seven to fifty-seven years of age. They are all keratinised, one of them very feebly.

This completes the list of tumours of columnar-celled mucous membranes that I have observed, part or the whole of the parenchyma of which was composed of squamous epithelium. The above remarks are based upon forty-four cases. Twenty-eight of these are pure cancroids, and sixteen adeno-cancroids. With but two exceptions all these neoplasms were malignant.

A cystic adenoma of the thyroid and a papillary adenoma of an accessory thyroid are the only members of the series whose behaviour was innocent. I have not included in this list five carcinomata of the endometrium whose structure is open to doubt, or a number of mammary tumours that will require further study. It will be seen that, although tumours with heterotopic squamous epithelium are rare, they are by no means rare enough to form pathological curiosities. This is especially true of the uterus, the gall-bladder, and the air-

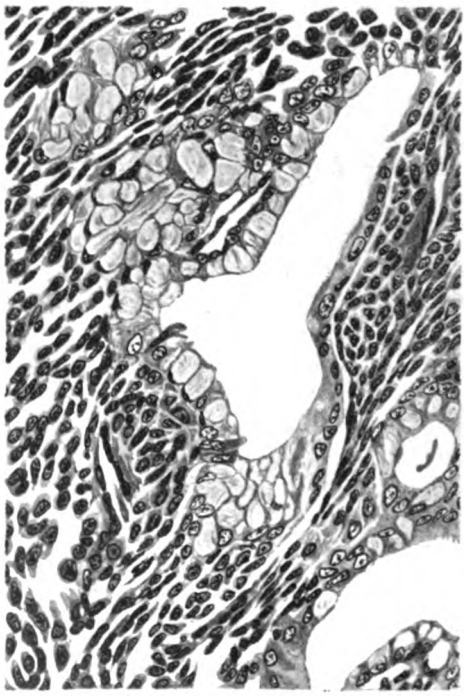

FIG. 74.

Basal-celled carcinoma of skin containing goblet-cells. Magnif., 350.

sinuses, the carcinomata of the last of which contain this tissue in the majority of cases.

It is therefore of interest to note that the converse obtains, although very much more rarely. It is quite exceptional for a squamous carcinoma of the skin to contain columnar epithelium as an essential constituent of its parenchyma. Schridde [67] has described and figured a case of this kind. In a non-keratinised epithelioma of the skin he found tubular structures with obvious lumina, lined by very tall, clear, cylindrical epithelium. Fig. 74 represents analogous

cells in a basal-celled carcinoma (rodent ulcer) of the skin of the mental region of a woman of thirty-five. Several glandular spaces are seen in the drawing, lined by large goblet-cells, which, as is proved by suitably stained sections, are distended with mucin. It is interesting to follow their manner of formation in other parts of the specimen. Cracks appear among the basal cells, upon the surface of which these become cubical and columnar. Glandular spaces are given off from them, whose lining is formed by the goblet-cells seen in the figure. There can be no doubt whatever that these cells are derived from the parenchyma of the tumour.

In my paper on " Heteromorphoses " [52] I drew attention to

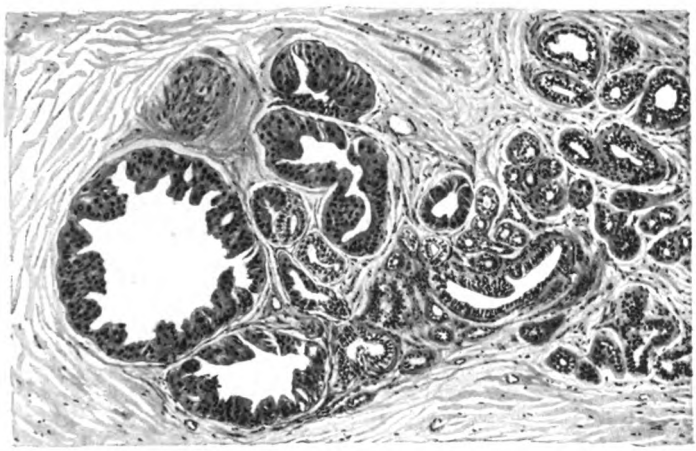

FIG. 75.

Mammary acini resembling sweat-glands in polycystic chronic mastitis. Magnif., 90.

the fact that metaplasia of one kind of columnar epithelium into another is possible, in the alimentary canal at least, and instanced gastric ulcers and a tuberculous appendix in support of this statement. Corresponding appearances are sometimes seen in tumours. Thus there is a type of duct carcinoma of the breast which closely resembles in structure the large axillary sweat-glands. Its cells are very large and distinctly eosinophile. In certain cases of cystic mastitis and occasionally in healthy organs identical cells are to be found lining ducts and secreting acini. Fig. 75 represents them. It was taken from a poly-, or, more correctly, a pan-cystic breast, in which there was marked hyperplasia of the epithelium. Ducts and tubules lined by these eosinophile cells are to be seen everywhere in the

breast. As the drawing shows, a part only of a tubule may be lined by them. These appearances preclude, to my mind, the possibility of an inclusion of displaced sweat-glands. Mammary carcinomata of this type have been and, as far as I know, still are explained upon the assumption that these glands, being from their heterotopic nature more prone to become blastomatous than normally situated tissues, are responsible for their formation. I have tried to show in these studies that there are no grounds whatever for this view. It is, indeed, reduced to an absurdity by cases like the one illustrated in Fig. 75, unless we grant that practically every lobule of the whole breast contained a displaced sweat-gland.

The type of epithelium under consideration has been used by Krompecher [37] in an attempt to show that the view, extensively advocated by certain French writers, is justified, that so-called polycystic "mastitis" is not of inflammatory origin, but a cystoma, or true tumour. The presence of these cells and of plain muscle fibres * indicates a hamartoma or faulty state of differentiation. The breast, which has evolved from a sweat-gland, has remained behind in places at a stage of development which corresponds with the latter. I admit that the view that these cases of cystic mastitis are hamartomata contains the truth. They are "tumour-like malformations," which is, as we have seen in Study IV., Albrecht's definition of hamartomata. But I fail entirely to see the smallest grounds for the assumption that they must be caused by arrests of development, faulty states of differentiation, or any other kind of congenital malformation. Following upon what I have said in Study IV., I regard them as typical tumour-like overgrowths of mammary tissue that have arisen in "acquired" tissue malformations. Even though Krompecher [37] is no doubt perfectly right when he maintains that the fibrosis and round-celled infiltration always seen in these cases are secondary, and not the results of a primary inflammation or "mastitis," he considerably oversteps the known facts when he concludes that they must therefore necessarily be secondary to a congenital malformation. Is it not far more probable that they are, in most cases at all events, secondary to and caused by the atrophy and involution that are physiological at the period of life at which "chronic mastitis" is most common? These are essentially *senile* changes.† They are, it is true, quite as much a part of the life history of the mammary glands as their development in the embryo, and

* I cannot speak of the latter from personal experience.

† Since this view is, after all, generally accepted, I need not defend it here.

quite as inevitable. But nevertheless they are not congenital malformations in any conceivable meaning of the word.

I have one more objection to Krompecher's [37] statement that the presence of epithelium of the type of sweat-glands is a sign of incomplete differentiation of the breast. The only clue we have of the stage of differentiation a tissue has attained is the nature of the secretory activity of its cells. This is, no doubt, more complex in the breast than in the sweat-glands, but certainly differs essentially in these organs. It is therefore wrong to say that the presence of epithelium resembling sweat-glands indicates a reversion to a lower type on the part of the

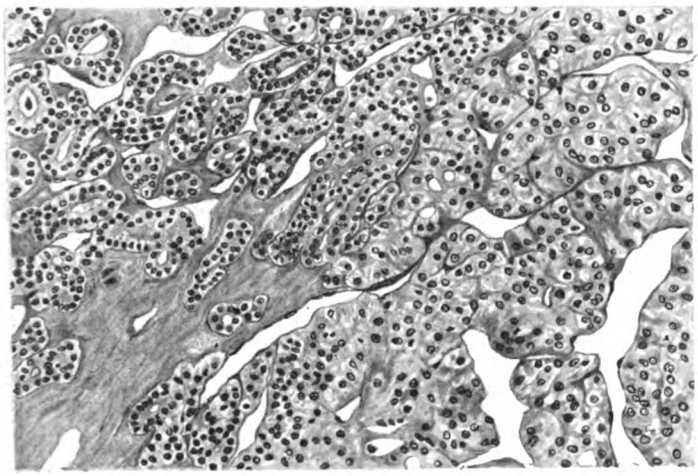

FIG. 76.

Carcinoma of thyroid, partly parathyroid and partly thyroid in structure. Magnif., 180.

mammary gland. The truth is, surely, that it indicates the assumption of a different kind of secretory activity, one naturally performed by a distinct, although closely related kind of epithelium. I look upon the presence of these glands as an additional proof that the breast is a modified sweat-gland.

Fig. 76 represents part of a large infiltrating carcinoma of the thyroid gland of a woman of fifty-two. Its greater part has the anatomical structure of parathyroid tissue. At the centres of some of its nodules the stroma is increased in amount and hyaline. Here the epithelial cells of the tumour have assumed the structure of thyroid tissue, with the formation of vesicles containing colloid. At the edges of the hyaline stroma a zone of intense proliferation of the epithelium is present, in which the nuclei are increased in number and reduced in size, and many

mitoses are present.* It appears from the anatomical relations of the tumour that its original structure is parathyroid, but that a metamorphosis into typical thyroid tissue has taken place in its older parts. I cannot venture to give an opinion if this be antecedent to or consequent upon the hyaline changes of the stroma. Nor is it possible to state whether the neoplasm has arisen in thyroid or in parathyroid tissue. All that the specimen demonstrates is that its cells have undergone differentiation in both these directions. To me the tumour appears to give some support to the work of Forsyth [15] and to his conclusion that the thyroid and the parathyroid possess the same essential structure and an identical histiogenesis, even if we are not prepared to agree fully with his [16] statement that "the parathyroids are essentially thyroidal in nature, possessing no peculiar functions, but engaged in the active secretion of the same substance as the thyroid gland."

It may be said that I ought to have included the specimen under consideration, and even more so the parathyroid adenoma within the thyroid described in Study I. (Fig. 5), among the choristo-blastomata enumerated in Study V. This I have not done partly for the reasons I have just given, and partly because of the fact demonstrated by Forsyth,[15] that parathyroid tissue is to be found normally in practically every part of the thyroid.

If we now review all the tumours I have discussed in this paper, we find that they all consist either wholly or in part of an epithelium whose structure differs fundamentally from that of the cells of the organs in which they have originated.

When we come to discuss the histiogenesis of these heterotopic tumours, we are faced in our attempts to explain it, as practically everywhere else in morphology, with the two contending old views: "Preformation" and "Epigenesis"; views that have exercised men's minds for many a generation. Cohnheim [8] adopted a preformationist view. His theory explains heterotopic tumours, as well as new growths in general, as the result of an embryonic cell-rest, or a congenital malformation in its widest sense.† Because of an error of development, cells have reached the part that were predestined, on account of their ontogenetic history, to undergo differentiation in a certain direction, which is heterotopic at the spot to which they happen to have strayed, but would have been normal at the place at which they should have remained. If I have not

* These are all "clumped," and are represented in the drawing as irregular black dots.

† *Vide* Study II. p. 196.

already brought forward sufficient evidence in these studies to show how slight the foundations are upon which this theory rests, I despair of doing so. Personally I regard every preformationist theory not only as non-proven, but as reduced to an absurdity and thereby disproved, and shall therefore cease to give it serious consideration in future studies. In the present one I have, unfortunately, still to say a few words later on about Herxheimer's [23, 24] modification of Cohnheim's theory, which he has brought forward to explain heterotopic tumours.

An epigenetic theory as applied to heterotopic tumours assumes that the structure of the cells of a part is a "function of position." In other words, cells do not undergo differentiation in a given direction because they must obey their destiny, preordained from the beginning. They do so in response to an orderly sequence of stimuli, constituting the normal environment. Provided that this be of the right kind, development must inevitably proceed in the appropriate, or normal, direction. Should the orderly sequence be interrupted, development must as inevitably proceed in a new direction which, although "abnormal," is, as a matter of fact, the only one appropriate for the new or abnormal environment. I have entered fully into this question in my former paper,[52] in which I have attempted to show how an abnormal environment, acting during or long after embryonic development, gives rise to heterotopic tissues. If we apply these arguments to our tumours, we experience no difficulty in explaining the heterotopic cells they contain as caused by one of these heteromorphoses.

I have, following Schridde,[66] divided the heteromorphoses of epithelium into the congenital heteroplasias and the post-developmental or "accidental," as they may well be named, metaplasias. The former appear to me to be no more "predisposed" to tumour formation than the normally differentiated cells of the body. The best known of them is the "upper cardiac glands" of the œsophagus, at the level of the cricoid cartilage in 70 per cent. of human beings. Of the few columnar-celled carcinomata of the œsophagus that are on record not one, to the best of my knowledge, has ever been described at this level. Again, we know of not a single instance of heteroplasia of the epithelium of the gall-bladder. The only case in which squamous epithelium was found in this viscus, without a coincident neoplasm, is that of Lubarsch,[41] in which it was associated with a granuloma. The inference that it was caused by an inflammatory process, and that it is therefore an instance of metaplasia, is obvious. It is true that

we know of one example of an apparent heteroplasia of the ducts of the pancreas, that of Herxheimer.[24] Against this we must place Kawamura's [32] case of distomiasis of the pancreas and liver, with extensive metaplasia of the epithelium of the duct of Wirsung and of its medium-sized branches into squamous epithelium.* Yet again, squamous epithelium has been found very rarely within the normal body of the uterus, and then only in children. The best instance I know of, of this condition, has been recorded by v. Friedlaender.[18] One side of the uterus of an otherwise healthy girl of five, who had died of scarlet fever, was lined, from just above the internal os to near the fundus, by a large patch of squamous epithelium. Uterine glands were absent at its centre, but had been converted into cysts beneath its periphery, where their ducts were covered by the squamous epithelium. A few small isolated islands of this tissue were present around the circumference of the big patch. The connective tissue was normal, except for the presence of a few isolated leucocytes. Although v. Friedlaender mentions the possibility of this anomaly having been caused by a hæmorrhage, I think there can be little doubt, because of the state of the connective tissue and of the presence of cystic uterine glands beneath the squamous epithelium, that it was of long standing, and therefore what we call a heteroplasia in the absence of a clue of the manner of its production. Squamous epithelium has never been found in the healthy endometrium of adult women. Hitschmann,[27] indeed, went so far as to say that, when the uterus is lined by squamous epithelium this is always atypical, and to be regarded as suspicious of malignancy, if not as already malignant.

Metaplasia, on the other hand, because of the very nature of its causation, readily explains the heterotopic epithelia of our tumours. For it is an atypical or heterotopic regeneration, a re-differentiation, a result of an active proliferation caused by inflammatory processes.

It appears to me that we must separate as sharply as possible the concepts "heteroplasia" and "metaplasia," especially since the latter is far from being universally admitted by pathologists. Most of us seem to take the view that heteroplasias can be admitted, since everything is possible within the uterus, whereas re-differentiation of fully differentiated cells is quite inadmissible. The views of biologists are more advanced and, if I may say so, sounder in this respect. Several biologists I have discussed tumour formation with have expressed their astonishment that Cohnheim's theory should still be so widely

* There was no metaplasia of the bile-ducts in this case.

accepted. Since there is no argument so sure to convince others of the soundness of one's own opinions than that of quoting those of one much greater in their support, I venture here to translate part of Driesch's [10] analysis of the terms " differentiation " and " redifferentiation " :

" To be ' finished ' means, to be unable to undergo subsequent change from inner causes without the help of a disturbance of form. According to this definition an organ can be finished in one sense, and yet react adaptively to external stimuli in as many ways as necessary * (p. 84).

" Everything that is known to be unfinished is ' protophase,' is embryonic in the strict sense of the word.

" Everything that is ' embryonic ' undergoes differentiation; it must undergo it.†

" Everything that is finished changes its form or regenerates, it can undergo re-differentiation or regeneration.

" These sentences are the logical sequences of the fact that we have called everything ' embryonic ' that still produces something else in every case, even without a disturbance, whereas that was called ' finished ' which, under the same conditions, as surely produces nothing new " (p. 83).

In his Gifford lectures Driesch [11] makes these statements: " There are more morphogenetic possibilities in each part than the observation of the normal development can reveal. If at each point of the germ something else *can* be formed than actually is formed, why then does there happen in each case just what happens and nothing else? In these words indeed we may state the chief problem of our science " (p. 87). " We speak of secondary restitution whenever a disturbance of organisation is rectified by processes foreign to the realm of normality; and these abnormal lines of events are revealed to us in the first place by the activity of potencies which remain latent in ontogeny proper " (p. 111). In speaking of the possibility of retro- or back-differentiation, ‡ of which little was known at the time, he says: " There may appear a very strange problem in its wake: the problem whether *all* morphogenesis might be capable perhaps of going backwards under certain conditions " (p. 164). §

* *E. g.* by metaplasia.

† This may be in an atypical direction and give rise to a heteroplasia.

‡ *I. e.* de-differentiation.

§ This would not be the place to criticise Driesch's philosophy were I able to do so properly. It appears to me, however, that he suffered from a defect not altogether unknown in biologists, in that he knew no pathology. Had he drawn a less sharp distinction between primary regulations, " that lie at the root of true embryology," and those that he called secondary, " whereby a disturbance is rectified by a process foreign to the realm of normality," it is possible that his views would have been less vitalistic.

It is mainly to Child [7] that we owe our knowledge of how extensive de-differentiation can be, at all events in the lower animals. This author, however, maintains in common with others that in adult mammals one type of cell never changes into another. I have discussed this question in my former paper [52] (p. 123), where I tried to show that the statement is incorrect, since metaplasia is a true de-, followed by re-differentiation. I shall revert to this question at the end of this paper.

My object in making this digression has been to point out that, upon the evidence of eminent biologists, there is no reason at all to assume that perfectly normal cells cannot, when suitably stimulated, give rise to heterotopic tissues by a process that we speak of as "metaplasia." The fact seems to me to be of some biological importance. Physiologists have long realised to the full that adaptations of function are of everyday occurrence. But can a change of function ever take place without a corresponding change of morphology? I believe this to be impossible. As Driesch has beautifully expressed it: "Structure is a function of position" (des Ortes). This implies that structure and function are inseparable; they are body and soul, if I may use these expressions. The change of structure that corresponds with one of function may be so slight, it is true, as to be imperceptible with the means at present at our disposal. It is possible that it may in some cases never be appreciated. It is, however, a suggestive fact that, with improved methods, the list of "functional" disorders is becoming smaller and smaller. The metaplasias are of importance, since they are changes of function in which the associated changes of structure are apparent.

I take an epigenetic view of development and growth, both physiological and pathological, if these terms be permissible. They are certainly inaccurate, in my opinion, since the adoption of such a view instantly raises the question: Can growth ever be pathological in its essential nature? If we believe that every effect (structural and functional) has its cause, and that it depends absolutely upon and varies with the latter, we are forced, it seems to me, to adopt the view that every reaction that takes place is, and of necessity must be, physiological, since it is the only possible reaction for the given environment. We are at perfect liberty to speak of pathological or abnormal causes, in the sense that they are unusual, but their effects are always predictable or, to be accurate, could be predicted with sufficient knowledge. They are therefore strictly physiological or normal, in the true sense of the word, in every case, from the moment of the union of the gametes to form the zygote, to the

death of the latter in extreme old age. It appears to me that the doctrine of predestination must, of logical necessity, be accepted up to this point.*

It must be granted that it is quite as much an inherent biological property of the cells of the body to proliferate as it is to functionate. Cells, like the individuals they form, but too readily follow the line of least resistance.† A tumour can, therefore, be spoken of as abnormal simply in the sense of being a reaction to an unusual stimulus, or to the absence of a normal one. I must leave the detailed consideration of this point for a future study. Here I wish merely to point out that, if the comparatively slight amount of proliferation of chronic inflammation can favour an atypical or metaplastic regeneration and re-differentiation, this is much more likely to occur during the almost unlimited growth of the cells of a tumour. This I take to be the reason why metaplasia is commoner and more extensive in tumours than in organs that are merely in a state of chronic inflammation.

All these considerations bring us back to the point that there are no valid reasons against the view that heteromorphoses are produced by cells that were perfectly normal at one period of their life history. When applied to tumours this formula can be expressed thus : there are no reasons against the assumption that heterotopic tumours originate in the epithelial cells of the organ in which they are found. Their histiogenesis is, therefore, identical with that of typical carcinomata of these organs.

This is the place to refer to Herxheimer's [23, 24] views concerning the histiogenesis of heterotopic tumours. He believes that a true metaplasia, or heterotopic re-differentiation of differentiated cells, does not take place in the adult body. He admits that a displacement of an epidermal or squamous cell-rest is impossible in organs like the gall-bladder or the pancreas. The explanation he offers is this : certain cells of the part have failed to undergo full differentiation, but have retained the original potency of the germinal layers to undergo a belated differentiation into one or all the kinds of cell into which the latter are differentiated. Heterotopic tumours are, therefore, according to him, a delayed form of heteroplasia caused by a congenital anomaly of certain cells of the part. But, apart from the fact that he merely puts back the anomaly, because of which normal differentiation was inhibited, into embryonic life, and

* This is as far as we need, or indeed *can* go in a paper upon tumours. To argue that causes must be equally inevitable would be to leave scientific for metaphysical reasoning, with which we have no concern.

† A perfectly logical statement, and one that follows from those made in the preceding paragraph.

thereby saves himself the trouble to inquire into its cause,—for a cause must surely have acted to produce this effect,—Herxheimer's theory suffers from another, and greater, disadvantage. He fails to show that these undifferentiated cells exist or can, indeed, exist. His views are as unsatisfactory and, to my mind, as unsatisfying as all those based upon a preformationist doctrine.

This brings me to the consideration of the relative frequency of heterotopic tumours in different parts of the body. It has often been stated that they, or that metaplasias, at all events, are most frequently met with near the surface of the body and in organs that are in contact with others lined by squamous epithelium. But is this really so? It is true enough of the nose, as has been shown by Schoenemann,[64] and of the accessory sinuses. It is equally true of the larynx. Kanthack[31] demonstrated many years ago the extreme ease with which metaplasia into squamous epithelium takes place in this organ. But then this change occurs with almost equal, if not with equal freedom in the smaller bronchi (McKenzie[43]). It appears, therefore, that mere proximity to a squamous mucous membrane is not of itself sufficient to explain the frequency of the presence of heterotopic epithelium in the respiratory tract. Again, the body of the uterus is separated by the length of the cervical canal from its *os externum*, where the vaginal squamous epithelium normally ceases. On the other hand, cancroids of the stomach and rectum are exceedingly rare. Mere proximity, therefore, does not account for their frequency. It might be urged, as has indeed been frequently done, that undifferentiated cells, in the sense of Herxheimer,[24] are most likely to be present in numbers near these orifices. Our brief review of the facts has shown us that there is little support for this view. It might, of course, be argued on the other side that the mucous membrane of the stomach is too highly differentiated to allow of the ready occurrence of metaplasia. There are two answers to this. It is difficult to see why undifferentiated cells, to whose presence this change is attributed, should not be present in a highly differentiated organ as well as in one whose structure is more simple.* Again, although I freely admit that the mucous membrane of the stomach is highly differentiated, I fail to see why that of the rectum should be more so than the endometrium or the nasal mucous membrane, since they are all essentially conducting surfaces. Indeed, if we take function as our

* The statement that cells near a squamous surface are "predisposed" to acquire the structure of those of the latter is no more than a restatement of a possible fact in other words.

criterion of differentiation, the endometrium is by far the most highly differentiated of the three. Does not the frequency of heterotopic tumours within the uterus support the view that heterotopic epithelium is a form of atypical regeneration, since its mucous membrane is in a constant state of violent regeneration at regular intervals for a period of many years? Is it not reasonable to assume that this regeneration occasionally goes wrong and becomes atypical?

There is yet one other point to be considered. Does the heterotopic epithelium of our tumours arise within the neoplasm after it has been established, or is it the result of metaplasia of the cells of the mucous membrane antecedent to tumour formation? I can dismiss these questions in a few words, since there is very little evidence that enables us to give a positive answer to them. As I have pointed out on several occasions, we simply do not know the conditions that were present at the spot before the tumour had appeared, and which led to its formation. Both possibilities are realised, no doubt. The gall-bladder has frequently been found to be lined by squamous epithelium when it was the seat of a new growth (*vide supra*), whereas it has been seen but once apart from a neoplasm. This suggests; although it is far from proving, that this change was the first in time to take place. It does not, of course, prove in any way that heterotopic epithelium is more disposed to blastomatous growth than normal epithelia. All that it shows is the well-known fact that irritated and actively proliferating cells are disposed to tumour formation. It also shows that in the gall-bladder, at all events, the formation of squamous epithelium is an indication of a degree of proliferation closely akin, if not identical with blastomatous growth. Since heterotopic tumours in general are commoner than the corresponding "simple" metaplasia, they appear to suggest that the cause that induces them acts upon cells that already form part of an established neoplasm.

Excursus.—We now come to what I believe to be the point of chief interest, not so much in a pathological as in a biological or even philosophical sense, of heterotopic tumours, and especially of metaplasias in general. I here refer to the "purposiveness" displayed by them in common with other vital phenomena, to an apparent realisation of a desired effect, which it is hard to explain upon scientific lines. For there can be not the slightest doubt that the conversion of columnar epithelium into that of the squamous variety, when bathed by irritating inflammatory discharges, is a most beneficial change. Squamous

epithelium is constructed to resist these, it is " meant " to resist them, whereas columnar epithelium readily succumbs to them by being macerated and disintegrated. It would thus appear that the cells undergo metaplasia for the sole and express purpose of prolonging their lives.*

What is meant by the word " purpose " ? If I desire a given end, I use certain persons or tools as my more or less unconscious agents in bringing it about. I direct their actions for my own use. When the end desired by me is attained, my purpose has been served. My actions have been " purposive," whereas my tools have only been " useful." A purpose thus necessitates the presence of a guiding influence outside the matter upon which it acts (Driesch [11]).

Must we apply this concept to the manifestations of life, as we see them in the body ? Before attempting to answer this we must try to form some idea of what we mean by " life." We can begin by asking a further question : Is life the sum total of all the reactions and interactions of all the cells of the body explainable (or ultimately explicable in the light of a wider knowledge) in a manner strictly comparable with those that are at work in chemical and physical processes, even though they be infinitely more complex than these, or must we assume a something in addition to them, a something that is new and cannot be explained as their summation ?

Both these lines of inquiry bring us to the same point. Must we explain vital phenomena as the manifestations of a new principle, of a " biological or vital category " (J. A. Thomson [72]) which is, strictly speaking, outside the tissues of the body, and need not necessarily be influenced by the ordinary laws of chemistry and physics ? Must we assume that this new principle exerts a guiding action upon the natural reactions of the body ?

To do so would be wrong, since we should then leave the realms of science for those of metaphysics and theology, where purely scientific methods no longer avail. We must, it seems to me, limit ourselves to strictly scientific arguments. It is the object of science to find one single ultimate principle in all things.† To invoke the aid of new categories merely to suit our purpose is therefore wrong, since it rapidly leads us into the outer darkness of purely inductive reasoning.‡ And

* The benefit the mesenchyme derives from the change is, of course, purely secondary, and in no sense of the word " teleological."

† Its aim is not so very different, after all, from that of pure theology.

‡ By this I mean that, without facts to guide us, we are in danger of imitating the sage who derives inspiration and wisdom solely from the contemplation of his umbilicus. There is no reason why his speculations should not be sound enough, but there is no guarantee of their soundness.

may it not be said of us that to create new categories is, after all, essentially a sign of false pride, and a barefaced attempt to hide our colossal ignorance?

Not only would it be wrong to assume the presence of a new guiding principle in vital phenomena, but it is unnecessary to do so. Such a principle demands some rudimentary form of consciousness, to the extent at least of knowing the end to which its actions are directed. But cannot this "foreknowledge" be explained more simply and scientifically by the needs of the whole, by chemical and physical changes set up in the body? These stimulate directly the cells concerned in the production of the apparently teleological effect by altering their immediate environment. To this they react in the only possible manner, provided they have the potency so to react.

It is here, I think, that we begin to realise the true biological importance of metaplasia and allied changes undergone by the differentiated tissues of the body in response to alterations of their environment. They are built up of living cells. If we pursue our analysis of what we mean by "life," it seems to me that it can be explained, in part at least, as an "instability," an endless series of reactions and interactions readily performed in answer to changes in the medium, whereby numerous and different, more complex substances are constantly built up, and as constantly broken down again into less complex ones. These changes are of such variety that they are limited only by the original "historical" composition of the protoplasm which gives the cells their "specific" stamp. Within these limits they are all possible at all times. During ontogeny progressive changes are undergone in one direction. They are known as "differentiation," and because of them more and more stable substances are gradually accumulated. These vary in different tissues and give them their characteristic structure, because of which they perform their proper functions. This general increase of stability depends, to my mind, upon the harmonious interaction of all the parts of the body, designated by the name of "normality." * Because of it the number of changes, all of which are potentially possible at all times, is strictly regulated. But when the normal balance is upset, the cells react in many ways, whose extent and direction is again limited by the new or abnormal equilibrium that has been established. One kind of reaction is proliferation. The potency to divide rapidly which becomes less and less in most cells as development proceeds, once more becomes evident at the expense, as a glance at actively proliferating granulation tissue instantly tells us, of

* This category is, of course, purely epistemological.

their differentiation. In other words, the more stable and recently formed substances that have accumulated are broken down again more or less completely. The cell as a whole becomes less stable. Since "instability" is, according to our definition, one of the attributes of life, its body now contains more "living" substance, and is therefore more truly alive. The cells become younger. They undergo a true rejuvenescence, and approach once more an embryonic condition. It seems to me that these facts, insisted upon by Child,[7] are too self-evident to be denied. The cells become less differentiated *de facto* as well as in appearance. This can only mean that some of their earlier potencies are reacquired. And now, if we grant, with Driesch, that structure is a "function of position," we can see how it is that squamous epithelium is produced in the ventricles of the brain or in the gall-bladder in post-embryonic life. If "position" means the sum total of the influences exerted by the environment, it follows that this may change to the extent of necessitating the formation of stable substances of a different kind from those originally present, whereby a different or heterotopic cell is produced. The changes of environment that lead to metaplasia are of the nature of irritants, which tough squamous epithelium is much better able to resist than delicate cylindrical cells. One of the original alternative prospective potencies is thus reawakened. In fact it is re-acquired, in the true sense of the word.*

What appears at first sight a "purposive" act can thus, I believe, be reduced to a mechanical *adaptation* to an alteration of environment. In the fact that metaplasia is a "regulation" in the sense of Driesch [10] I see its chief biological importance. For it is a very simple change, one in which but one kind of tissue is involved at a time.† It is also as good an experiment as many devised by the most skilled operators, since it is clearly the effect of the injury, or disturbance of equilibrium that results from inflammatory irritation. I maintained in my paper upon "Heteromorphoses" that metaplasia is a form of regeneration. This I still believe, and can see no essential difference between it and the regeneration of a whole limb in a newt, for instance. The differences that exist are merely differences of degree.‡ The stimulus to regeneration is, in both

* I was not prepared last year to go so far as this; *vide* [52], p. 124.

† It has been the fate of the slight "tissue" malformations to have fallen between two stools. They are unknown to anatomists and biologists, and treated as curiosities by pathologists.

‡ I realise fully how great these are. But this is not the place to discuss them, were I qualified to do so. I simply wish to point out that the potency to regenerate cells of a different kind has not been entirely lost in one of the highest mammals, contrary to the statements I have seen in all the books upon biology I happen to have read.

cases, the needs of the body. If it is, as I believe, a quality of living substance to build up the whole from its parts, provided that the environment permit it, and the needs of the body demand it, then regeneration, from the very simplest kind to the reconstruction of a large part of the body, loses much of its mystery. After all, we all of us subscribe to the old dogma "*omne vivum ex ovo.*" So where is the insuperable difficulty in our accepting the view that a substance that was once present can reappear if it be needed? Does not this take place every time a new individual is produced, be there a "continuity" of the germ-plasm, or be there none? All that we must assume is that the living substance is really and truly "alive," and not the sort of half-animated machine, theories like that of Weismann [75] would have us believe. I can thus see no reason for the assumption that true purposiveness exists in biological phenomena.* A serious objection to my hope and belief that vital processes are reducible and will some day be reduced to the same laws as chemistry and physics is thus overcome.

These opinions may brand me a confessed materialist in the sight of many. But for this I care nothing, since I can find no meaning in the name. For it seems to me that chemistry and physics even are not to be explained entirely by chemical and physical laws, and that every philosophy that demands the action of a vital principle in animate nature, be it the *spiritus rector* of the ancients, or an *entelechy*, as it is understood in modern times, loses sight of the fact that it is nothing new, and that the same principle is at work throughout inanimate nature. The fact that the union of two atoms of hydrogen with one of oxygen always gives birth to a new molecule of the same old substance—water, and always with an explosive energy unheard of in the ontogeny of animate beings, is a true expression of "life," and requires the same "foreknowledge" of what is to be. A something is at work everywhere in nature, call it what we please, ὃ ἔχει ἐν ἑαυτῷ τὸ τέλος.

What more are the actions and reactions we call the vital force or principle, or ἐντελέχεια, than an ἀνάγκη, a universal stern necessity? Its manifestations are immutable and unfailing; every science and every common act of daily life depend upon it alike; yet the why and the wherefore of its action remain the mystery of mysteries. Surely, it is good science humbly to accept an ultimate principle in all things, when we despair of explaining it. But as surely is it bad science to invoke new principles or categories merely to suit our own convenience.

* Except in so far as the simplest chemical reaction is "teleological," in the sense of being constant in a given environment.

Conclusions

The cells of " heterotopic " tumours have a different essential structure from those of the tissue or organ of origin.

Heterotopic cells constitute either the whole or only a part of the parenchyma of these tumours.

Their histiogenesis is to be explained by metaplasia, a de-differentiation, followed by an atypical re-differentiation of differentiated cells and not by displaced cell-rests or other congenital malformations.

Other tumours, that appear to be heterotopic at first sight, are the result of prosoplasia or of simple changes of form. Since they are preceded by differentiation only, they must be separated from those that are truly heterotopic.

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THE LÆVULOSE TOLERANCE TEST FOR HEPATIC EFFICIENCY, AND ITS APPLICATION IN CERTAIN TROPICAL DISEASES *

By GORDON COVELL, M.D., Captain, I.M.S.

In 1921 Maclean and De Wesselow [1] pointed out that the only sugar in ordinary use the consumption of which did not produce a rise in the blood-sugar concentration was lævulose. They showed that in a normal healthy adult 50 g. of lævulose could be taken without any appreciable increase in the blood-sugar.

In the same year Spence and Brett,[2] using Maclean's method, published the results of a series of cases in which this test was applied. From these they concluded that in a subject with diminished liver efficiency a definite rise in the blood-sugar resulted from the ingestion of lævulose, the height and length of the " blood-sugar curve " portraying this rise being in proportion to the degree of liver inefficiency present; and they claimed that the test afforded a means of estimating the degree of liver damage in cases of toxic salvarsan jaundice and other diseases of the liver.

So far as I am aware, the test has never before been applied in cases of tropical disease. In dealing with these, the question as to whether the liver is affected or not is constantly arising, especially in connection with amœbiasis.

It was felt that a reliable test which would indicate not only the presence of some hepatic inefficiency, but also the degree of the damage to the liver, would be of especial value in the diagnosis and treatment of tropical diseases.

The aim of the work which forms the subject of the present paper was twofold.

(1) To confirm the results and conclusions of previous workers on the subject, while using a different method of sugar estimation.

(2) To apply the test in such cases of tropical disease as were accessible in this country, and to compare the results so obtained with those found in non-tropical cases.

With these objects in view a series of tests was carried out

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by the writer on a number of patients in Guy's Hospital and in the Hospital for Tropical Diseases, Endsleigh Gardens, the results of which are analysed below.

In order to control the results, the test was also applied to a number of normal individuals.

Details of the Test

The test was carried out in each case four hours after the patient had taken a light breakfast.

The amount of lævulose given was on the following scale :—

To a patient weighing	12	stone	. . . . .	50 g.
,, ,,	9	,,	. . . . .	40 g.
,, ,,	7	,,	. . . . .	35 g.

The amount of blood-sugar was estimated immediately before giving the lævulose, and again at intervals of one and two hours after its ingestion.

The method of sugar estimation was that of Folin and Wu,[3] 1 c.cm. of blood being taken from a vein for each estimation.

At the suggestion of Dr. J. H. Ryffel, this method was modified as follows. For the preparation of the phosphate molybdate solution, Folin and Wu use molybdic acid, which is boiled with caustic soda to free it from ammonia. The molybdic acid which we obtained contained very little ammonia, but gave an unsatisfactory colour. We therefore substituted ammonium molybdate, boiling it with caustic soda till free from ammonia.

In other respects the method employed was as described by Folin and Wu, except for the following modification in the calculation. When the 0·1 per cent. and 0·2 per cent. standard dextrose solutions are compared with the colorimeter, it is found that the latter always gives a reading rather more than twice that of the former. A correction is therefore necessary.

The following example makes this clear.

Supposing that, when matching the unknown (X) against the 0·1 per cent. standard, and the 0·1 per cent. standard against the 0·2 per cent. standard, the readings are as follows :—

1 part of X equals 1·28 of the 0·1 per cent. standard, and 1 part of the 0·2 per cent. standard equals 2·20 of the 0·1 per cent. standard.

That is to say, X in the terms of the 0·1 per cent. standard equals 0·128, and the 0·2 per cent. standard in the terms of the 0·1 per cent. standard equals 0·220.

Subtracting 0·1 from each of these, we get 0·028 and 0·120 respectively.

The corrected result is then :—

$$X \text{ equals } 0{\cdot}1 + \frac{0{\cdot}028 \times 0{\cdot}1}{0{\cdot}120}$$

i. e., X contains 0·123 per cent. of sugar.

Analysis of Results

The cases will be considered in four groups.

Group A. Normal individuals.

Group B. Patients suffering from various general diseases.

Group C. Patients with clinical evidence of hepatic disease, other than tropical cases.

Group D. Cases of tropical disease.

Group A. Normal Individuals

In Table I are summarised the results of the test as applied to presumably normal individuals. They were chiefly students at Guy's Hospital.

TABLE I.

Serial No.		Age.	Blood-sugar per cent.		
			Before lævulose.	1 hr. after.	2 hrs. after.
1	G.C.	35	0·114	0·126	0·117
2	J.M.	24	0·107	0·113	0·110
3	M.M.	24	0·106	0·114	0·103
4	A.O.	29	0·124	0·129	0·121
5	F.B.	26	0·109	0·115	0·112
6	D.W.	22	0·123	0·126	0·118
7	J.M.	25	0·113	0·118	0·113
8	F.M.	28	0·115	0·118	0·108
9	G.D.S.	26	0·113	0·117	0·110
10	G.M.S.	25	0·106	0·117	0·116

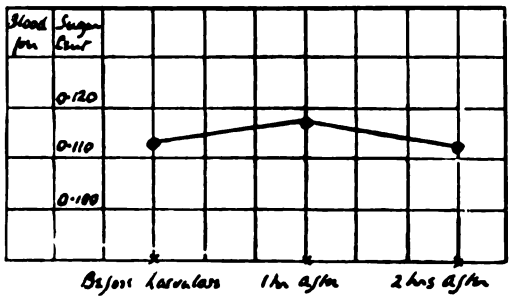
It will be seen that, whereas there is in each case an increase in the blood-sugar concentration after one hour, the rise is very slight, in no case amounting to more than 0·012 per cent. (12 mg. per 100 c.cm.). At the end of the second hour the amount of blood-sugar has fallen to the original level or thereabouts.

These results have been combined, and are shown in the form of a curve in Chart I, which is taken to represent the average normal curve. The highest curve in the series (No. 1) is shown in Chart II.

Interpretation of Abnormal Curves

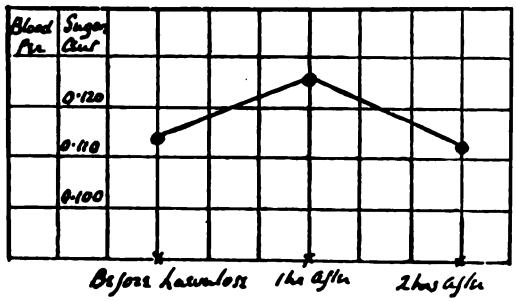
From the consideration of the results of the cases presented in this paper, it has been found that alteration in the lævulose tolerance causes an increase in the height and in the length of the curve. In classifying the results both these factors are taken into consideration, an increased figure at the end of the

Chart I.



Average "Normal" Curve.

Chart II.



Highest "Normal" Curve.

second hour being of more significance than a rise after one hour which falls to the original level after two hours.

This agrees with the conclusions formed by previous workers.

For purposes of comparison, the "average normal curve" is shown as a dotted line in all the charts which illustrate cases of lævulose intolerance.

Group B. General Medical Cases

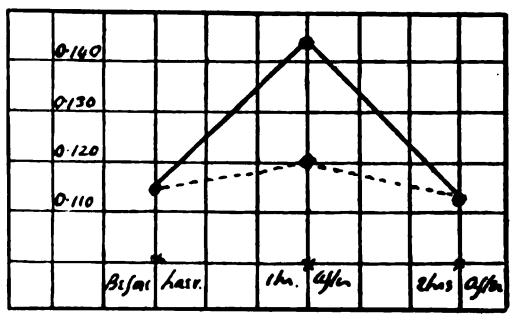
These were taken at random from the general medical wards. In none of them was there any clinical evidence of hepatic disease. The results are summarised in Table II.

TABLE II.

Serial No.		Age.	Disease.	Blood-sugar per cent.			Result.
				Before lævulose.	1 hr. after.	2 hrs. after.	
11	A.B.	44	Chronic Bronchitis. Alcoholism.	0·115	0·143	0·111	Slight liver inefficiency.
12	E.A.	39	Bronchiectasis.	0·128	0·130	0·125	Normal.
13	H.W.	30	Tuberculous Peritonitis.	0·111	0·129	0·119	Very slight liver inefficiency.
14	R.B.	49	Addison's Anæmia.	0·099	0·103	0·097	Normal.
15	A.V.	49	Neoplasm of small intestine.	0·131	0·137	0·130	Normal.
16	J.B.	61	Arteriosclerosis. Epilepsy.	0·127	0·149	0·148	Moderate liver inefficiency.
17	A.D.	21	Colitis.	0·107	0·113	0·109	Normal.
18	H.T.	21	Fibrositis.	0·116	0·120	0·110	Normal.
19	C.S.	35	Gastric Ulcer.	0·117	0·132	0·121	Normal.
20	A.P.	40	Fibroid Phthisis.	0·117	0·123	0·122	Normal.
21	Y.	35	Malaria.	0·106	0·114	0·107	Normal.
22*a*	J.B.	38	Peripheral Neuritis (arsenical).	0·080	0·120	0·116	Marked liver inefficiency.
22*b*	„	„	24 days later.	0·099	0·129	0·115	Moderate liver inefficiency.
23	A.S.	44	Diarrhœa (*Spironema eugyratum* in stools).	0·117	0·126	0·116	Normal.

Of the cases shown in Table II, it will be seen that nine show no abnormal rise in the blood-sugar. The remaining four, which show varying degrees of intolerance to lævulose, will be considered in greater detail :—

CHART III.



Case 11.—Chronic Bronchitis and Alcoholism. Slight liver inefficiency.

Case 11 showed a slight degree of liver inefficiency, the rise in the blood-sugar being 0·028 per cent. after one hour, falling to normal at the end of the second hour (Chart III).

Although there was no clinical sign of hepatic disease, the

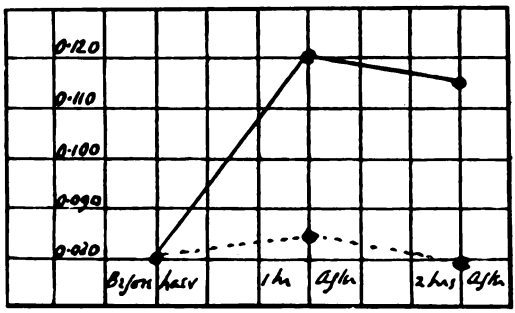
man was a heavy drinker, and it might therefore be assumed that there was some degree of cirrhosis of the liver.

Case 13 showed a very slight degree of liver inefficiency, the rise in the blood-sugar being 0·018 per cent. after one hour, falling to normal after two hours. This patient had previously been in hospital for cholecystitis.

Case 16 showed a moderate degree of liver inefficiency, the blood-sugar rising 0·022 per cent. after one hour, and remaining at almost the same level at the end of the second. This was rather an obscure case. The patient suffered from hallucinations and persistent headache, and there was a history pointing to attacks of epilepsy while a young man.

This was the only case in the whole of my series in which the test was distinctly positive, and in which there seemed to be

CHART IVA.



Case 22.—Peripheral Neuritis, following arsenical poisoning.

no justification for assuming that there was any hepatic inefficiency apart from the result of the test. In the light of the results obtained in the rest of the series, it may perhaps be suggested that there was some defect of the liver in this case also, possibly a condition of senile atrophy.

It may be noted in passing that C. M. Wilson [4] has found that Widal's hæmoclasic crisis test gave a positive result in the majority of epileptics. This case was the only one in my series with a history of epilepsy.

Case 22 showed a marked degree of liver inefficiency, the rise in the blood-sugar amounting to 0·040 per cent. after one hour, and remaining almost as high after two hours (Chart IVA).

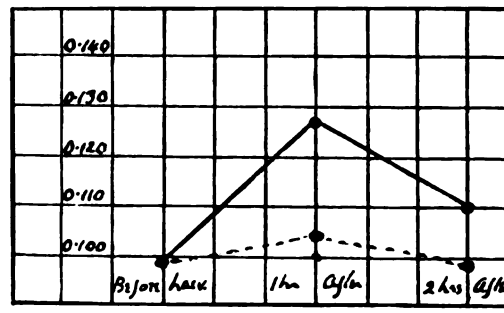
The test was repeated 24 days later, and showed that the liver had recovered to a certain extent. This time the rise was only 0·030 per cent. after one hour, while at the end of the second

hour the blood-sugar was only 0·016 per cent. above the original level (Chart IVB).

The man was a West Indian negro, suffering from severe peripheral neuritis, the result of arsenical poisoning, which dated from nine months previously. He stated that he had never been jaundiced, and at the time of his admission to hospital the liver was not appreciably enlarged. The marked intolerance to lævulose exhibited in this case suggests that the liver tissue had been seriously damaged by the toxic effects of the arsenic.

This case affords a striking example of the value of the lævulose tolerance test in indicating liver inefficiency in the absence of any clinical evidence.

CHART IVB.



Case 22.—24 days later.

Case 21 is of interest as showing the value of a negative result of the test in certain instances. The patient, a Lascar, had a temperature of 100° F., and complained of severe pain in the region of the liver, so that it was at first suspected that he might be suffering from liver abscess. Three days after the test had been applied with a normal result, benign tertian malarial parasites were found in the blood, and following the administration of quinine the temperature fell to normal, and all the symptoms disappeared.

GROUP C. PATIENTS SHOWING CLINICAL EVIDENCE OF HEPATIC DISEASE OTHER THAN TROPICAL CASES

These cases are summarised in Table III. It will be noticed that in every case, with the exception of Cases 33 and 36, there was an abnormal rise in the blood-sugar concentration following the administration of lævulose.

TABLE III.

Serial No.		Age.	Disease.	Blood-sugar per cent.			Result.
				Before lævulose.	1 hr. after.	2 hrs. after.	
24	N.K.	28	*Syphilis.* Gumma of scalp. Liver and spleen enlarged.	0·113	0·127	0·134	Moderate liver inefficiency.
25	E.H.	24	*Syphilis.* Periostitis. Liver palpable.	0·102	0·118	0·110	Very slight liver inefficiency.
26	N.K.	24	*Catarrhal Jaundice.* 14 days after onset.	0·100	0·122	0·103	Slight liver inefficiency.
27*a*	J.S.	21	*Acute Hepatitis.* 14 days' pyrexia. Liver enlarged. No jaundice.	0·130	0·143	0·157	Marked liver inefficiency.
27*b*	,,	,,	12 days after cessation of fever. Liver not now palpable.	0·113	0·118	0·112	Normal.
28	C.N.	28	*Banti's Disease.* Spleen enlarged, liver palpable.	0·127	0·171	0·148	Marked liver inefficiency.
29	F.C.	45	*Malignant Disease of Liver.* Ascites.	0·112	0·133	0·129	Moderate liver inefficiency.
30	W.E.	56	*Malignant Disease of Liver.* Ascites.	0·127	0·164	0·158	Marked liver inefficiency.
31	D.C.	61	*Cirrhosis of liver* (Alcoholic).	0·140	0·176	0·171	Marked liver inefficiency.
32	J.B.	44	*Banti's Disease.* Spleen very large. Ascites.	0·115	0·151	0·142	Marked liver inefficiency.
33	J.H.	64	*Obstructive Jaundice.* 3 weeks' history.	0·143	0·150	0·138	Normal.
34*a*	E.W.	23	*Toxic Salvarsan Jaundice.* 7 days after onset.	0·106	0·117	0·162	Severe liver inefficiency.
34*b*	,,	,,	3 weeks later.	0·106	0·128	0·106	Slight liver inefficiency.
35	P.	53	*Cirrhosis of Liver.* Ascites.	0·100	0·128	0·123	Moderate liver inefficiency.
36	E.S.	63	*Gastritis.* Liver just palpable. ? Cirrhosis.	0·103	0·114	0·109	Normal.
37	M.S.	46	*Slight Salvarsan Jaundice.* 5 days after disappearance of icterus.	0·114	0·146	0·111	Moderate liver inefficiency.

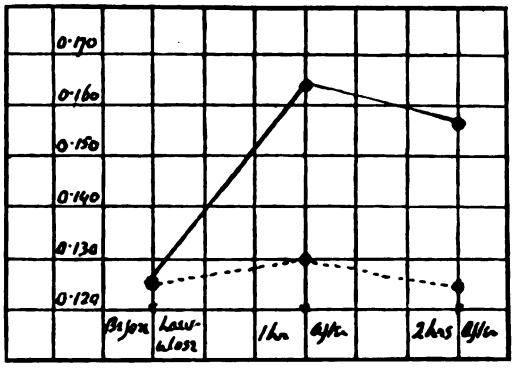
Charts V and VI illustrate two of the cases in Table III.

Case 30 was that of a patient suffering from carcinoma of the stomach, with secondary deposits in the liver and ascites. He died in the hospital, and at the autopsy the liver was found to be very extensively infiltrated with growth.

Case 34 showed the most severe intolerance to lævulose of all. This patient had had thirteen injections of silver salvarsan.

Symptoms of intense jaundice, vomiting and anorexia commenced about three weeks after the last injection. The liver was palpable 2 in. below the costal margin.

CHART V.

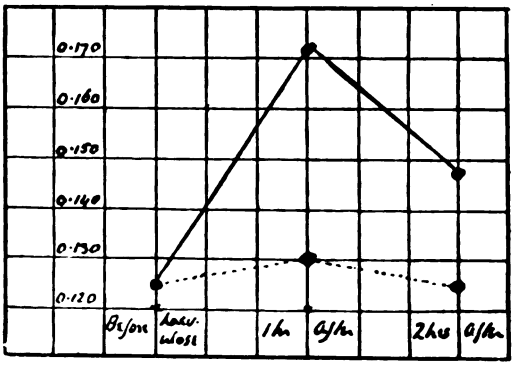


Case 30.—Malignant Disease of Liver. Marked hepatic inefficiency.

The rise in the blood-sugar after one hour was only 0·011 per cent., but after two hours it had risen to 0·057 per cent. above the original level.

The test was repeated three weeks later, when, although the

CHART VI.

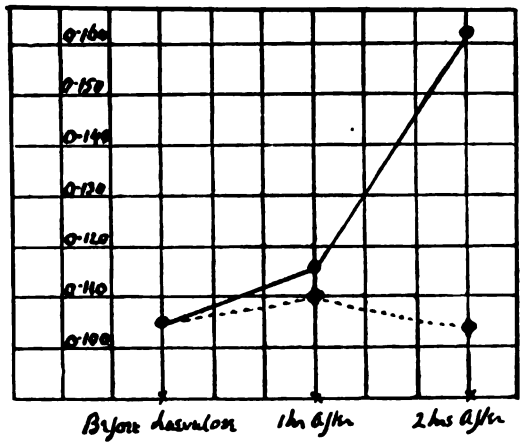


Case 28.—Banti's Disease. Marked liver inefficiency.

liver was still markedly enlarged, the jaundice had very greatly diminished, and the other symptoms had disappeared. Only a slight degree of intolerance was revealed, the rise being 0·022 per cent. after one hour, and the blood-sugar falling to its original level after two hours.

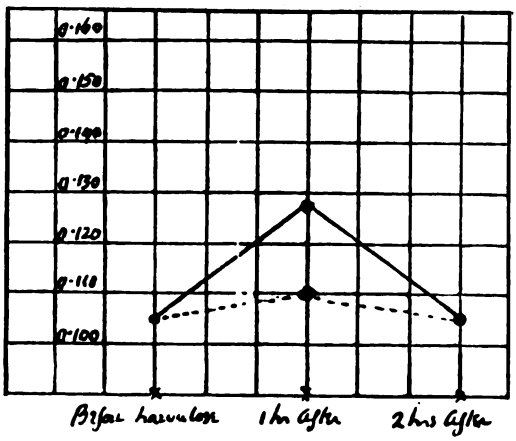
Charts VIIA and VIIB illustrate this case :—

CHART VIIA.



Case 34.—Toxic Salvarsan Jaundice. Severe liver inefficiency.

CHART VIIB.



Case 34.—3 weeks later. Slight liver inefficiency.

Case 33 forms a marked contrast to the last. Jaundice had come on gradually during the previous three weeks, and the liver could be palpated as low as the umbilicus. The lævulose test resulted in a normal curve.

The patient died in hospital, and at the autopsy the common bile-duct was found to be obstructed by fibrosis of the head of the pancreas.

Case 36 was that of a patient aged 63, who was admitted with a history of abdominal pain and vomiting coming on from one to two hours after meals. There was also a doubtful history of hæmatemesis. The liver was just palpable, and the

man admitted that he had taken a good deal of alcohol. This led to a tentative diagnosis of cirrhosis of the liver. If this diagnosis was correct, it illustrates a case in which the lævulose tolerance test failed to indicate hepatic inefficiency when disease of the liver was present. The patient continued to have severe abdominal pains while in hospital, but otherwise his condition improved, and he had put on several pounds in weight when he was discharged.

Group D. Cases of Tropical Disease

1. *Results of the Test in cases of Sprue*

All the cases summarised in Table IV were cases of chronic sprue which had been under treatment for some months, and were all progressing favourably.

TABLE IV.

Serial No.		Age.	Blood-sugar per cent.			Result.
			Before lævulose.	1 hr. after.	2 hrs. after.	
38	A.W.	64	0·094	0·125	0·119	Moderate liver inefficiency.
39	A.J.	27	0·098	0·118	0·090	Slight liver inefficiency.
40	R.E.	50	0·087	0·098	0·089	Normal.
41	J.A.	59	0·105	0·119	0·110	Normal.
42	W.B.	53	0·091	0·111	0·101	Slight liver inefficiency.
43	D.W.	45	0·111	0·113	0·108	Normal.

As will be seen from Table IV, three of these cases gave a normal result, two showed a very slight degree, and the other a moderate degree of liver inefficiency. As this latter patient (Case 38) also gave a markedly positive Wassermann reaction, the result may have been due to a syphilitic affection of the liver.

The results, so far as can be deduced from so small a series of cases, point to the conclusion that there is no considerable degree of hepatic inefficiency in cases of chronic sprue.

2. *Results of the Test in Amœbiasis*

These results are summarised in Table V. In the investigation of this disease the lævulose tolerance test has proved of very considerable value. It is possible to state definitely by its means whether the liver is involved or not. Further, in cases of amœbic hepatitis, by applying the test before commencing treatment and repeating it after the completion of the course, it is possible to ascertain whether the treatment has or has not been successful in restoring the efficiency of the liver.

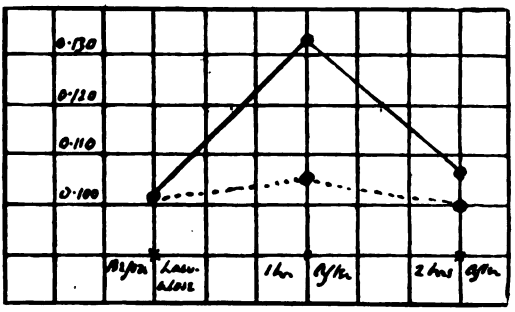
TABLE V.

Serial No.		Age.		Blood-sugar per cent.			Result.
				Before lævulose.	1 hr. after.	2 hrs. after.	
44	R.A.	44	History of Amœbic Dys. Liver palpable.	0·114	0·156	0·121	Moderate liver inefficiency.
45	C.L.	41	*E. hist.* cysts had been found before treatment. None now present.	0·126	0·132	0·132	Normal.
46	B.H.	46	Amœbic liver abscess, 7 days after aspiration.	0·101	0·135	0·104	Moderate liver inefficiency.
47	R.T.	35	History of Dysentery. Stools negative.	0·106	0·116	0·106	Normal.
48	L.H.	33	*E. hist.* cysts in stools. Liver just palpable.	0·108	0·124	0·114	Very slight liver inefficiency.
49*a*	G.W.	31	*E. hist.* cysts in stools. Liver just palpable.	0·108	0·122	0·115	Very slight liver inefficiency.
49*b*	,,	,,	23 days later, after treatment. Cysts absent.	0·116	0·123	0·115	Normal.
50*a*	A.R.	46	*E. hist.* cysts in stools. Liver just palpable.	0·103	0·122	0·105	Slight liver inefficiency.
50*b*	,,	,,	26 days later, after treatment. Cysts absent.	0·133	0·139	0·131	Normal.
51*a*	E.F.	40	Free *E. hist.* in stools. Liver 1½ in. below ribs.	0·140	0·202	0·158	Marked liver inefficiency.
51*b*	,,	,,	21 days later, after treatment. *E. hist.* cysts still present.	0·114	0·144	0·123	Moderate liver inefficiency.
52*a*	J.S.	21	Free *E. hist.* in stools. Liver palpable.	0·102	0·129	0·114	Slight liver inefficiency.
52*b*	,,	,,	14 days later, after treatment. Cysts absent.	0·118	0·125	0·115	Normal.
53*a*	L.P.	22	Free *E. hist.* in stools. Liver not palpable.	0·118	0·145	0·130	Slight liver inefficiency.
53*b*	,,	,,	16 days later, after treatment. A few cysts still present.	0·102	0·105	0·102	Normal.
54*a*	C.H.	30	Free *E. hist.* in stools. Liver palpable.	0·111	0·133	0·125	Slight liver inefficiency.
54*b*	,,	,,	16 days later, after treatment. Stools negative.	0·115	0·119	0·116	Normal.
55	E.D.	30	History of Amœbic Dys. Stools negative.	0·121	0·137	0·121	Very slight liver inefficiency.
56	H.B.	36	History of Dysentery and several attacks of jaundice. Stools negative.	0·117	0·150	0·132	Moderate liver inefficiency.
57	A.H.	30	History of Dysentery. Stools negative.	0·120	0·138	0·131	Slight liver inefficiency.
58	S.T.	32	*E. hist.* cysts had been found before treatment. None now present.	0·109	0·119	0·109	Normal.

One point of interest has been brought out by this investigation, viz. that in amœbiasis the liver is affected much more frequently than has hitherto been supposed.

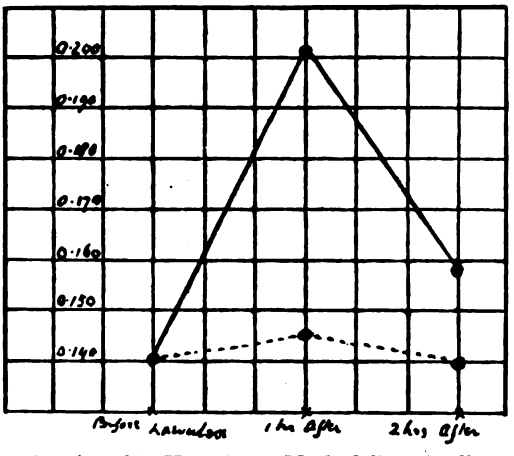
In every case in which either the cysts or the free forms of *Entamœba histolytica* were present in the stools at the time when the test was applied, a certain degree of hepatic inefficiency was

CHART VIII.



Case 46.—Liver Abscess, 7 days after aspiration.

CHART IXA.



Case 51.—Amœbic Hepatitis. Marked liver inefficiency.

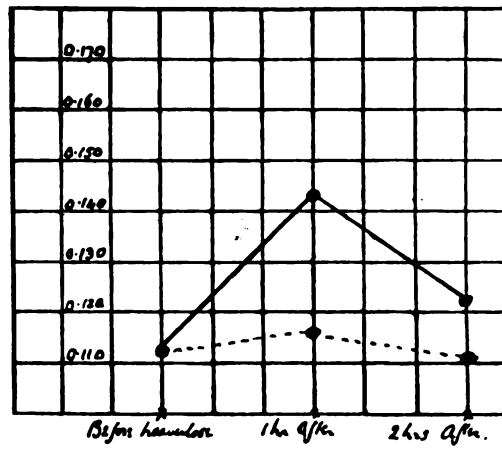
revealed. The only exception to this was Case 53 (*b*), when after a course of treatment the test gave a normal result, although a few scanty *E. histolytica* cysts were still present in the fæces.

Unfortunately I have not yet had the opportunity of applying the test in the case of a patient with a liver abscess before operation, but it seems probable that it would be of great value in determining the diagnosis in a doubtful case.

Case 45 was of special interest. On admission to hospital *E. histolytica* cysts were present in the stools, and there was a tumour in the region of the epigastrium, which suggested the possibility of an amœbic liver abscess.

After a course of treatment with emetine no more cysts were found in the stools, but the tumour remained. The lævulose test gave a normal result. Subsequently an operation was

CHART IXB.



Case 51.—21 days later, after treatment. Moderate liver inefficiency.

performed, at which the tumour was found to be an epigastric hernia.

Charts illustrating cases 46 and 51 are shown above.

CONCLUSIONS

I. That the claims put forward by Maclean, Spence and Brett as to the value of the lævulose tolerance test as a means of estimating the efficiency of the liver are fully corroborated.

II. That, contrary to certain criticisms that have been made recently, the test forms a valuable indication of hepatic disease in certain cases where there is no clinical evidence of damage to the liver. And, further, that it is of value in chronic as well as in acute cases of liver disease, though the response is less marked in the former.

III. That in cases of chronic sprue there is no considerable degree of liver inefficiency, so far as can be deduced from the few cases in which the test was applied.

IV. That in amœbiasis the liver is affected in greater or less degree in the large majority, if not in all cases. The test forms a very valuable means of detecting the degree of hepatic inefficiency in this disease, and of showing whether after a course of treatment the efficiency of the liver has been restored.

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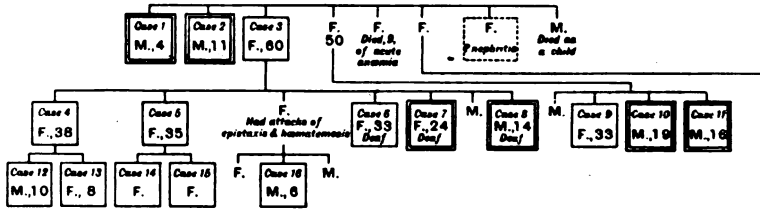
HEREDITARY FAMILIAL CONGENITAL HÆMORRHAGIC NEPHRITIS

OCCURRING IN SIXTEEN INDIVIDUALS IN THREE GENERATIONS

By ARTHUR F. HURST, M.D., Physician to Guy's Hospital.

IN the *Guy's Hospital Reports* for 1912 I published an account of a family three members of which in one generation and eight in the second generation suffered from hæmorrhagic nephritis. In the eleven years which have elapsed since then two more cases in the second generation have died, and five cases have developed in the third generation. It therefore seems worth while bringing the tree up to date, and at the same time completing the literature of the subject by reference to four families subject to nephritis, in addition to those of Dickinson and Attlee mentioned in my original paper.



The above tree is of a family, three or four out of eight members of which in one generation, eight out of twelve in the next generation, and at least five out of eight in the third generation suffered from nephritis. Those enclosed within a square were affected, whilst the others, so far as I am aware, were unaffected. Those enclosed in double squares died, presumably from the disease. For the details of Cases 3, 5, and 8 I am indebted to a paper by the late Dr. Leonard G. Guthrie, read before the Harveian Society of London on April 24, 1902,[1] and he furnished me with further details about Cases 8 and 12. Dr. Langdon Brown has had Cases 12, 13, and 16 under his observation, and kindly gave me some additional information about the family tree. Case 10 was under the care of Dr. Kendall of Battle during his last illness, and he also sent Case 11 to see me; for the account of the death of Case 11 I am indebted to Dr. K. H. Stokes of Bexhill. The incomplete notes regarding the other cases are derived from what the mother of Cases 9, 10, and 11 has told me.

Case 1.—A male, the eldest of the first generation, died when four years old, after having had albumen and blood in his urine. The cause of death is not known.

Case 2.—A male, died when eleven years old, after having had albumen and blood in his urine. The cause of death is not known.

Case 3.—Female, 60 years old, the mother of Cases 4, 5, 6, 7, and 8, said in 1902 that as long as she remembered she had been subject to attacks of hæmaturia similar to those of her children. They were always produced by eating black currants and drinking claret, and also accompanied various slight ailments. The last occasion on which severe hæmaturia occurred was in 1896, shortly after the birth of her youngest child. She always appears to be well, and is active and energetic.

Case 4.—Female, 38 years old, has been subject to attacks of hæmaturia, but is now apparently well.

Case 5.—Female, 35 years old, has had albuminuria at least since the age of 12: the urine has also always contained traces of blood detected on microscopical examination, fragments of blood casts, but no hyaline or granular casts. When 13 years old, a week after she had had for a few days a severe sore throat, she was violently sick, her tongue was dry, and her temperature rose to 102° F.; she complained of headache and passed bright scarlet urine. The temperature gradually fell, and the urine regained its normal appearance in about a fortnight. There was never any œdema, the heart was normal in every way, and the kidneys were not palpable. Black currants are said to have induced similar attacks of hæmaturia. She is now free from symptoms.

Case 6.—Female, 33 years old, is subject to attacks of hæmaturia, which can always be brought on by the consumption of black currants.

Case 7.—Female was subject to attacks of hæmaturia, which could always be brought on by the consumption of black currants. She died when 24 years old.

Case 8.—Male died in 1910, aged 14 years, from acute pericarditis. His urine was never completely free from albumen and blood. It was always red and never smoky in appearance. Blood casts, but no hyaline casts, were present. At any rate up to the age of 12 there were no cardiovascular abnormalities. Every two or three months an attack lasting about a week occurred, in which

the amount of blood in the urine was greatly increased; slight malaise was present, and the tongue was furred. These exacerbations were accompanied by enuresis and frequency of micturition, and were often brought on by catching cold. Attacks also followed influenza, extremes of hot and cold weather, the consumption of strawberries and asparagus, but not black currants, gooseberries, raspberries or grapes. Even when severe hæmaturia was present, he was as "bright and merry as possible."

Case 9.—Female, 33 years old, has had albumen in her urine since she was three weeks old. There has never been any obvious hæmaturia, and her general health appears to be excellent. A specimen of urine examined in July, 1914, showed the presence of a small quantity of albumin and a few red corpuscles. The patient was not seen, but was said in 1914 to be in very good health. Now, however, in 1923, she is a chronic invalid and is subject to acute attacks of illness.

Case 10.—Male died in 1911, aged 19. He never had scarlet fever, and was accidentally discovered to have albumen in his urine after a football match when 14 years old. The albuminuria persisted, and attacks of hæmaturia frequently occurred after violent exercise, but he was a first-class cricketer and footballer. At Christmas, 1911, he had a bad attack of influenza; he played in a Badminton tournament before he had completely recovered and developed uræmia, from which he died.

Case 11.—Male, 16 years old, was discovered when two years old to have albuminuria; since then albumen has been found whenever the urine has been examined. In spite of this he was full of life and spirits and played games as well as any average boy until 1912. At that time there had never been any œdema; the kidneys were not palpable, and the heart was normal, but the blood-pressure was 143 mm. of mercury. The urine was always clear and there had never been blood visible to the naked eye; its specific gravity was 1010; 0·4 per cent. of albumen was present, and this was about the same quantity as four years before. Only a small deposit was produced on centrifugalisation; it contained numerous red blood corpuscles, the proportionate number of leucocytes, a small number of granular and hyaline casts, some excess of mucus and the normal urinary epithelial cells, but no renal epithelium, pus or other abnormality. When seen again in May, 1914, he had become extremely thin and anæmic. He had recently had several severe attacks of sickness. His heart was now considerably hypertrophied and the blood-pressure was 137 mm. The urine contained 0·23 per cent. albumen. The small deposit obtained on centrifugalisation contained several large coarsely granular and a few partly epithelial, partly fatty casts, several renal cells and a few red corpuscles. There was no retinitis. In July he had a short fit. He continued to be frequently sick and became progressively weaker. The urine then became scanty, and there was finally complete anuria; he became drowsy, but never lost consciousness completely. At the end his face was slightly puffy, but there was no œdema elsewhere. He died quite suddenly in his sleep at the beginning of August, 1914.

Case 12.—Male, 10 years old, had an attack of hæmaturia, lasting a few days, in December, 1913. In September, 1914, he had a sore throat with a temperature of 102°. The specific gravity of the urine was 1020; it contained albumen, blood and casts of all kinds. After six weeks only a trace of albumen was left; hyaline, epithelial and granular casts, leucocytes, red blood corpuscles, and blood-stained mucus were present. The blood-pressure appeared to be high, but was not measured; the heart was not hypertrophied, but a systolic murmur was heard in the mitral area, and the aortic second sound was accentuated. Now, in 1923, his urine is continuously abnormal.

Case 13.—Female, about 7 years old, has occasional attacks of hæmaturia without obvious impairment of health.

Cases 14 and 15.—Females, children of Case 5, both born since 1915. They have had slight attacks of hæmaturia, but appear to be otherwise healthy.

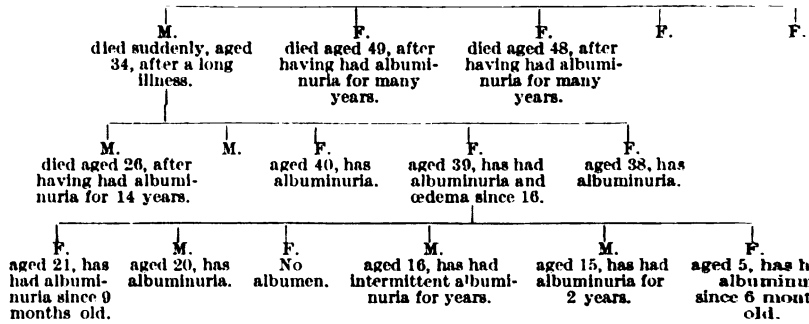
Case 16.—At least one child of the sister of Cases 4, 5, 6, 7, and 8, a boy, has signs of nephritis. She herself has had attacks of epistaxis and hæmatemesis, but has shown no evidence of renal disease.

I have called this condition "hereditary, familial, congenital, hæmorrhagic nephritis": hereditary, because at least three generations have been affected; familial, because it has attacked several members of the same family; congenital, because abnormal urine was discovered in one case when the patient was only three weeks old, in another when the patient was two years old, and in the remaining cases in early childhood and apparently on the first occasion that the urine was ever examined. "Hæmorrhagic nephritis" is, perhaps, open to criticism, but I think that the name corresponds better with the facts than "Congenital, hereditary, and family hæmaturia," under which Dr. Guthrie published his cases, for in Case 11 there was never any obvious hæmaturia, only traces of blood, insignificant when compared with the amount of albumen, having been found on microscopical examination. In several of the other

cases, moreover, albumen has been present without obvious blood in the intervals between the attacks of hæmaturia. Cases 10 and 11 died from uræmia, and Case 8 died of acute pericarditis, which may quite conceivably have been associated with nephritis. Unfortunately in no case was a post-mortem examination made. In Case 11 the unusually high blood-pressure and the cardiac hypertrophy in a boy of 16 pointed to the presence of definite nephritis, which was confirmed by the presence of hyaline and granular casts. It seems justifiable to call the nephritis hæmorrhagic, as most of the cases have been characterised by recurrent attacks of hæmaturia, the amount of blood passed in some cases being so great that the urine resembled that of a patient with renal calculus or a growth rather than nephritis.

When I first described this family in 1912 I could only find records of two other families affected in a similar manner. I have since obtained references through Dr. W. W. D. Thomson of Belfast to accounts of two additional families.

The following tree is that of a family, a description of which was published by Dickinson [2] in 1875.



Benson [3] in 1893 reported a series of four cases of acute nephritis occurring in the same family in a period of four years. The disease developed with œdema and albuminuria at the age of one year in two and in the others at four and three years respectively; the first died in uræmic convulsions after 3½ weeks, two others after about a year, the fourth being still alive at the time when the report was published.

Attlee [4] in 1901 described the history of three sisters, aged 5, 4, and 2, each of whom passed urine, which constantly contained albumen, often faint traces of blood, and occasionally granular casts; they suffered from intermittent attacks of hæmaturia, which were associated with malaise, and sometimes with vomiting and slight pyrexia. None of them showed any vascular changes. Their father had died at the age of 30 from uræmia.

In 1910 Fergusson [5] described a family, in which the father, aged 87, the mother aged 78, and eight children, whose ages varied between 45 and 56, had albuminuria, which was not, however, accompanied by any symptoms.

Since my paper appeared, W. W. Thomson and H. F. Macauley [6] reported four cases of acute nephritis occurring after influenza in a family of eight children. All four recovered completely. As nephritis was a comparatively rare complication in the influenza epidemic, they suggest that these children possessed a "familial predisposition to renal disease, an intrinsic weakness causing a *locus minoris resistentiæ* in the kidneys, the extrinsic cause of the nephritis being supplied by the influenza toxin."

John Eason and Malcolm Smith of Edinburgh have just reported a somewhat similar group of cases occurring at the same time in four members of a family, the infection on this occasion being apparently streptococcal and located in the naso-pharynx.

I have recently had under my care a man of 50 with severe generalised atheroma and signs of chronic nephritis. His father and one brother had died from acute exacerbations of chronic nephritis. His blood gave a negative Wassermann reaction. In this case the widespread vascular disease was perhaps the inherited factor which predisposed to the nephritis.

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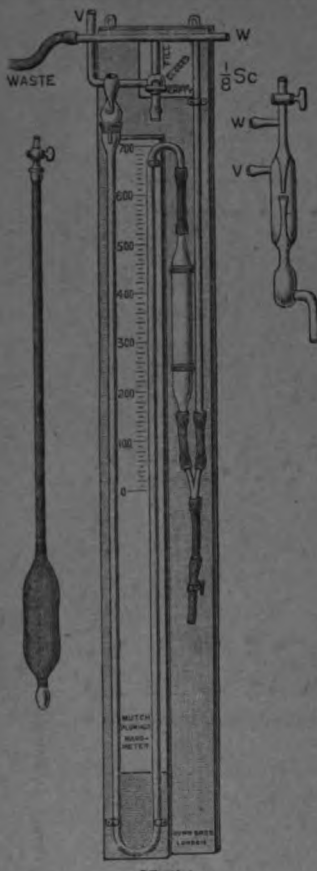

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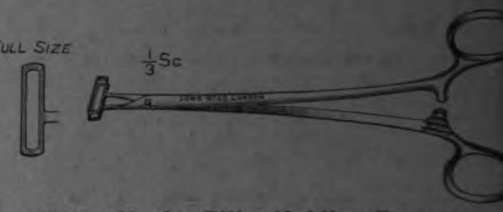

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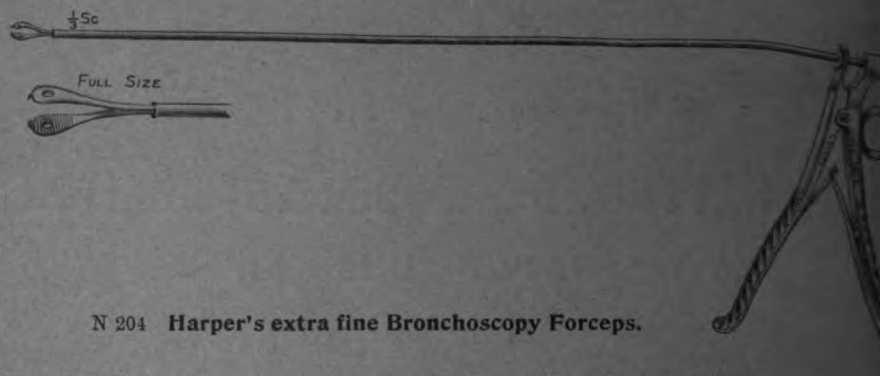

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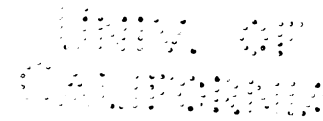

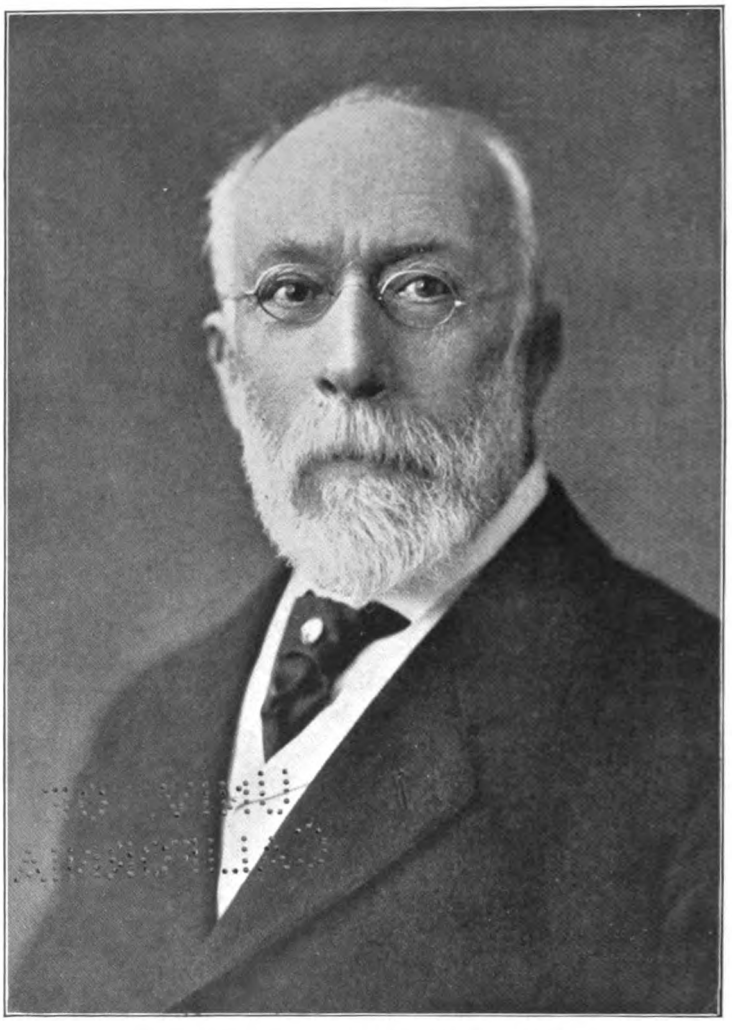

SIR GEORGE SAVAGE, M.D., F.R.C.P.

BORN 1842. DIED JULY 5TH, 1921.

SIR GEORGE H. SAVAGE, M.D., F.R.C.P.*

BORN 1842: DIED 1921.

By R. PERCY SMITH, M.D., Consulting Physician for Mental Disorders, St. Thomas's Hospital.

BY the death of George Henry Savage on July 5, 1921, at the ripe age of seventy-eight, English psychiatry lost one of its most widely known representatives, English medicine one of its most remarkable personalities, and large numbers of the profession and the public a most trusted friend and counsellor.

The writer has been privileged to have access to records left by Savage himself of his parentage and early life, which cannot fail to be of interest as showing the factors forming the mental " make-up " in such a distinguished man.

He was born in 1842.

Savage's father was a Yorkshireman, and is described as having been " a good horseman, a lover of sports, a good shot and skater." He entered into business as a druggist first at Balham and afterwards at Brighton, where he was the first to give anæsthetics for the Brighton surgeons about 1856, was chairman of the local Athenæum, became an alderman of the Borough and later a Justice of the Peace. He had a keen appreciation of science and for fifty years was a regular attendant at the meetings of the British Association. Savage described him as having an encyclopædic knowledge, as not profound in any science but interested in all, and as having made many interesting experiments.

Savage's mother was of Scottish birth, her maiden name being Wallace. In addition to being a deeply religious woman she was also a great reader. She recognised the value of cultivating observation and took up the study of English botany for the sake of her two boys. The summer holidays were often spent with them on the Sussex downs, " hunting out the names of the plants on the Linnean system " with the aid of botanical text-books. Savage's well-known love of botany was thus founded at a very early age.

His regard for her may be summarised in his own words: " She seemed to me to be the most self-sacrificing and best

* Reprinted by permission from the *Journal of Mental Science*, October, 1921.

woman I ever met. Her whole life was founded on the Christian faith." Savage learned to ride, skate and swim at an early age and this love of exercise and sport never deserted him. His experiences at various private schools at Brighton were not very happy. He described his last head master as having "no classical knowledge and no true scientific training," so that at the age of fifteen he had only read "the simplest Latin authors and no Greek beyond the Delectus." Nature study was, however, cultivated, and having already some knowledge of botany he soon took the lead. He and others ranged hills and dales within eight miles of Brighton and found birds' nests, flowers and forms of animal life; they yearly sent collections of wild flowers to a flower-show and generally obtained the prize. An assistant master, by name David Lyall, took a personal interest in him, which continued after he left the school and had a great part in shaping his future career.

At first Savage was destined to follow his father's business, but this was not congenial to him. However, during that time he did a great deal of practical chemistry, made the various gases, crystallised out most of the salts, and attended classes in chemistry at Brighton College, the teacher being Professor Bernays, subsequently Lecturer on Chemistry at St. Thomas's Hospital. Lyall, who was a frequent visitor at his father's house, stimulated him to work to become a medical man.

He then became apprenticed to a firm of doctors in Brighton, did dispensing and visited the Infirmary.

Lyall urged him to work for the matriculation of the University of London. This implied much very hard work at Latin, Greek, mathematics, etc., in which he was coached by Lyall and passed with honours in Botany.

He then entered as a pupil at the Sussex County Hospital, the House-Surgeon at the time being Mr. A. Willett, afterwards Surgeon to St. Bartholomew's Hospital. During the two years he spent there he still took a great interest in field botany and also used to go out at night for moths. "I think of some lovely nights spent in woods where the night side of nature was made plain to me." Nature in all its forms appealed to him, and he always regretted that fortune or chance never opened the path for original work to him in this direction.

In October 1861 he entered as a student at Guy's Hospital, living in modest rooms in Great Ormond Street because "it was nearer the College of Surgeons and other museums than Guy's," working very hard—never less than twelve and often sixteen hours a day.

At that time Moxon and Hilton Fagge were demonstrators

in the dissecting room, and among those on the staff were Hilton, Bryant, Habershon, Braxton-Hicks, Gull, Wilks, Bader, Cooper-Foster and Davies-Colley. Among fellow-students were Frederick Taylor, Howse and Mickley (afterwards Medical Superintendent of St. Luke's Hospital).

Savage was a terrific reader, and has recorded that " Moxon rightly gauged my mental type when he said that probably I read the biggest books on any subject, and forgot most but retained the essentials."

In due course he won the Treasurer's Gold Medal, qualified as M.R.C.S. in 1864 and L.R.C.P. in 1865. In the same year he graduated as M.B.Lond. and became House-Surgeon at Guy's Hospital. In the *Guy's Hospital Gazette*, January 31, 1903, Savage recorded many interesting memories of the past, such as the introduction of the thermometer and the ophthalmoscope, and his association with Gull, Wilks, Hughlings Jackson and Sutton, and recalled a forecast by Gull that it was possible there would be a time " when we should not only be able to see the back of the eye but ' right through people.' "

He was an active member of the Boating Club and a frequent swimmer at the Lambeth Baths.

His first association with Bethlem Hospital was in 1866, when for six months he held the post of what was then termed " resident student," being one of the second pair of qualified men thus appointed. Of this six months he wrote : " I believe that I alone saw the possibility which might open as a life's work." However, it was necessary that he should seek for remunerative work, and having been offered the post of medical officer to a lead-mining company at Nenthead, Cumberland, at a fixed salary, with horses and house provided and liberty to do general practice as well, he went there. The practice was of the most strenuous kind. He attended 500 confinements in four years; there were many cases of goitre and of miner's phthisis, an outbreak of smallpox to cope with, and occasional accidents. On one occasion he had to amputate a leg unaided and to stop in the middle to do artificial respiration, the anæsthetic being given by the unskilled brother of the patient. He constantly had to ride over the fells on winter nights, but his vigorous constitution and athletic nature made light of this, and he revelled in climbing crags, sport on the moors, the botany of the district, and ski-ing over snow and icy roads, on one occasion sliding down a frozen road into the village at the tail of a cow which was rushing away in terror. The village " never forgot the doctor and the cow." On one occasion his bridle was seized at a turnpike, as " the last time you leaped the gate;

it must have been you as there is nobody else in the county who could do it." During this time he was reading hard for the London M.D., which he took in 1867.

He became engaged to Miss Margaret Walton, of Alston, and was married on September 9, 1868. A daughter was born in the following year, but in a few days after her birth his short first married life was terminated by the death of his wife from pulmonary embolism. This tragedy entirely changed the current of his life. For a time he went to Germany with a friend " to look for mosses," botany as usual having an absorbing interest for him. He was in practice at Nenthead for four years. Then a vacancy occurred at Bethlem Hospital, Dr. Henry Rayner, at that time Assistant Medical Officer, having been appointed as Superintendent to Hanwell Asylum. Savage applied for the vacant appointment, and was unanimously selected by the governors from over 100 candidates.

In 1872 he went into residence at Bethlem Hospital and thus began the career in which he became famous.

On his appointment to Bethlem Hospital Savage threw himself with characteristic energy into the work, read up all the literature of the subject, including most of the French and German journals, kept personal notes of all cases in addition to the statutory case-books, and inspired all who worked there to do the same. He also joined Klein's classes in physiology, working hard at preparing specimens and cutting sections, and made the most of the limited pathological opportunities at Bethlem Hospital by making microscopical preparations of morbid material. He was elected a member of the Medico-Psychological Association in 1873, and his name first appears in the *Journal of Mental Science* as attending a meeting in December 1873, under the Presidency of Dr. Harrington Tuke, among those present being Maudsley, Wood, Blandford, Langdon Down, Paul, Mickle, Rayner, Sutherland, Stocker and Rhys Williams. Savage showed sections of the spinal cord of disseminated sclerosis and general paralysis.

Soon after this appointment Dr. Thompson Dickson, Lecturer on Insanity at Guy's Hospital, died, and Savage was made his successor, and continued to act thus for thirty years, one of the joys of his life being his Guy's class.

He also attended regularly the meetings of most of the medical societies in London, and joined the British Medical Association, and later the Neurological Society of London as an original member.

Almost immediately after his appointment to the post of Assistant Medical Officer he began to write. To the *Lancet* in

1872 he contributed a paper "On Goitre," the result of his experiences in Cumberland, to the *Guy's Hospital Reports* in 1875 and 1877 papers on "The Insanity of Childbirth" and "Heredity in Mental Disease," and to the *Lancet* in 1875 on "Overwork as related to Insanity."

At the meeting of the British Medical Association held in Manchester in 1877 he read a paper on "Hysteria and Insanity," a digest of which appeared in the *Journal of Mental Science* for October, 1877 (vol. xxiii.).

In 1878 he took the Membership of the Royal College of Physicians. At the Annual Meeting of the Medico-Psychological Association in the same year (Dr. J. Crichton Browne, President) Savage was acting as Secretary *vice* Rhys Williams—who had been appointed a Commissioner in Lunacy—and was elected co-editor of the *Journal of Mental Science* in collaboration with Drs. Clouston and Hack Tuke on the retirement of Dr. Maudsley. He continued to act as one of the editors until 1894, a period of sixteen years.

The year 1878 also marks his appointment as Resident Physician and Superintendent to Bethlem Hospital in succession to Rhys Williams.

From this time onwards for many years the *Journal of Mental Science* and other journals teem with records of his activities not only in connection with our Association, but at the International Medical Congress, London, 1881 (at which he was Secretary of the special section), at the annual meetings of the British Medical Association, Liverpool 1883, Belfast 1884 (at which he was President of the Section of Psychology), Brighton 1886, Leeds 1889, Bournemouth 1891, London 1895 and 1910, the International Medical Congress, Washington, 1887, and the Royal Society of Medicine, Section of Psychiatry, 1912.

It would take too much space to enumerate all his papers in our Journal. He never hesitated to record individual cases which might interest others as well as himself—the effects of treatment and the pathological findings in fatal cases. He was specially interested in the question of marriage of neurotic subjects or those who had been insane.

In this connection may be mentioned his papers on "Marriage in Neurotic Subjects" (*Journal of Mental Science*, vol. xxix., p. 49), "Mental Disorders Associated with Marriage Engagements" (*Journal of Mental Science*, vol. xxxiv., pp. 394 and 467), and "On Insanity and Marriage" (vol. lvii., 1911). The "Alternation of Neuroses," on which he read a paper at the British Medical Association in 1886, also greatly interested him, and he pointed out the frequency with which such conditions

as migraine, asthma, hysteria, epilepsy or even diabetes alternated with insanity.

The question of criminal responsibility of the insane concerned him much, and he soon became known as an expert witness where insanity was pleaded as a defence in criminal cases. On the kindred question of "Drunkenness in Relation to Criminal Responsibility" he read a paper in 1886 (*Journal of Mental Science*, vol. xxxii.), pointing out the inconsistencies in medical opinion as to responsibility for acts committed during drunkenness. His paper on "The Plea of Insanity" (*Journal of Mental Science*, vol. xxxvii.), is an excellent summary of the then position with regard to criminal responsibility, and it and the subsequent debate in which Dr. Orange of Broadmoor took part are well worth study. Among communications on the pathology of insanity may be mentioned "Cases of General Paralysis with Pachymeningitis" (*Journal of Mental Science*, vols. xxix. and xxx.), "Cases of General Paralysis with Lateral Sclerosis of the Spinal Cord" (*Journal of Mental Science*, vol. xxx.), "Hæmorrhages in General Paralysis" (*Journal of Mental Science*, vol. xxxi.), "Hæmaturia, Maniacal Excitement and Hæmorrhagic Pachymeningitis" (*ibid.*), "Morbid Appearances from Hardening Nervous Tissue," communicated to the International Medical Congress, London, 1881 (*Journal of Mental Science*, vol. xxvii.), and "Punctiform Cerebral Hæmorrhage" (*ibid.*).

The individual care of the insane and his attempts to get at the seat of delusional states by prolonged personal interviews and endeavours to explain and re-educate into normal paths were notable long before the days of modern psycho-analysis, and he was characteristically untiring in this direction. In 1885 he had been elected a Fellow of the Royal College of Physicians of London and in 1886 he became President of our Association. His Presidential address, delivered at Bethlem Hospital, August 9, 1886, was "On the Pathology of Insanity" (*Journal of Mental Science*, vol. xxxii.). In it he said: "I feel that the great physiological workers, like Ferrier, Horsley and others, are only the engineers who are studying the machinery, while we in asylums have the much more difficult problem of studying the motive power." He discussed diseases of the brain and of the body leading to insanity, the alternation of neuroses and disorders of function, and said, "All bodily disease has its mental aspect." With reference to the treatment of delusions of persecution he said: "In some of these cases there are reasonable methods of treatment, and in several very unpromising cases I have hunted the hallucinations out of house and home."

And further—" Each of these convincing proofs has acted as a mental soothing draught, and in the end rest more and more complete has been gained and the patient has got well." During his Presidency he also read a paper on the practical subject " When should Homicidal Patients be Sent on Leave or Discharged? " and another, which excited much controversy, on " Whether there is ever Sufficient Reason for the Use of Strong Clothing and Side-arm Dresses." His claim was for freedom to use such restraint as he thought would give patients the best chance of recovery.

In 1887 he attended the International Medical Congress at Washington and opened a discussion on " Syphilis and its Relation to Insanity." An abstract of this is to be found in *Brain*, vol. x., from the *American Journal of Insanity*, October 1887, and in a paper read by him before our Association in November 1887 (*Journal of Mental Science*, vol. xxxiii.), entitled, " Notes on the International Congress, Washington." The relationship of general paralysis to syphilis had not then been fully established but he referred to cases of long-standing syphilis followed by general paralysis, ordinary cases of general paralysis with a definite history of syphilis, cases of local syphilitic nerve lesions, treated and apparently cured and afterwards developing general paralysis, and cases starting in the spinal cord (ataxic type). In the discussion he said : " The consensus of opinion seems to be that I was right in saying that some cases of general paralysis undoubtedly come from syphilis." The writer, however, well remembers that Savage was coming to the conclusion at that time that all general paralysis was due to syphilis, and not only due to the effects of overstrain as he had formerly taught.

During these years he had been a frequent contributor to the pages of *Brain*. In vol. i. of that journal, before it became the organ of the Neurological Society, he had published papers on " Acute Mania associated with Abscess of the Brain," and on " Uterine Displacement Corrected and Insanity Cured." In vol. ix. is a paper read by him before the Neurological Society on " Some of the Rélationships between Epilepsy and Insanity," and in vol. xi. he published " Two Cases of Insanity Depending upon Syphilitic Disease of the Arteries," and " Case of Epilepsy in which there are Periods of Automatism of a very well-marked Nature." During this period he was in constant touch with Hughlings Jackson, Ferrier, Bristowe, Horsley and other neurologists.

While at Bethlem Hospital he had become much sought for as a consultant in mental cases, and in 1888 he decided to

retire from the post of Resident Physician and enter into consulting practice, which he did, residing at first at 3, Henrietta Street, W.

An important event during his life at Bethlem Hospital was his second marriage in 1882 to a daughter of Dr. H. Gawen Sutton of the London Hospital. Mrs. Savage was a lady of great personal charm, and her advent was an enormous addition to the social amenities of the Hospital. The dances and other entertainments for the patients became delightful gatherings, and she was much beloved by all with whom she came in contact. A son was born in 1883 who eventually entered the medical profession.

Reference must be made to the " resident students " (now called house-physicians), two of whom were appointed every six months. Many of Savage's happiest memories related to these. He did all he could to make them interested in the work of the Hospital; no less than twenty of them subsequently became assistant medical officers or superintendents of various public and private asylums. L. E. Shaw subsequently became Physician to Guy's, F. C. Turner to the London Hospital, and B. Pitts, G. H. Makins, W. Tyrrell and J. B. Lawford joined the staff of St. Thomas's Hospital, and many were life-long friends. On Saturday afternoons the racket-court in winter and the tennis-courts in summer afforded opportunities for vigorous exercise, in which Savage himself always took part. Visits to the Convalescent Home at Witley enabled him to follow his old hobby of botany and he always encouraged others to take an interest in it. On his retirement from Bethlem Hospital his colleagues and former " students " entertained him at dinner and presented him with a silver rose-bowl. In addition to the class from Guy's Hospital he held special clinical classes for men preparing for the M.D. London, and was always ready to demonstrate in his inimitable manner to foreign and other visitors.

A special feature for some years was the Sunday morning round, at which Wilks, Bristowe and others were frequent attendants. He never kept his knowledge, experience and views under a bushel, and his daily morning visits to the wards were always made in company with his assistant medical officer and resident students, who therefore did not suffer from the absence of constant touch with their chief which is the misfortune in many large asylums.

In 1884 the first edition of his text-book, *Insanity and Allied Neuroses*, was published. This was reprinted in 1886, revised in 1890, was subsequently reprinted several times, and in 1907

a new and enlarged edition was published in association with Dr. E. Goodall, who was responsible for bringing the pathological section up to date. The book was essentially practical and clinical, was widely read, and for long was a standard text-book for students in the London School of Medicine.

On leaving Bethlem Hospital in 1888 he was made a member of the Governing Body, and to the end of his life took an active part in its deliberations and in all measures for the improvement of the Hospital and its opportunities for clinical instruction, such as the formation of an out-patient department and the arrangements for courses of lectures in connection with diplomas in psychological medicine. He had for long taken an active part in the management of the After-Care Association and continued to act as its Treasurer to the year of his death.

He had formed a considerable nucleus of consulting practice while at Bethlem Hospital, and after leaving this largely increased. There was, however, no diminution of his activities from the literary point of view. At the British Medical Association meeting at Leeds, 1889, he read a paper on "Massage Treatment in Insanity," at Bournemouth in 1891 on "The Influence of Surroundings on the Production of Insanity," and before our Association in 1892 on "Influenza and Neurosis" (*Journal of Mental Science*, vol. xxxviii.). There were also papers (British Medical Association, London, 1895) on "Insanity of Conduct," and in 1901 on "The Use and Abuse of Travel in the Treatment of Mental Disorders" (*Journal of Mental Science*, vol. xlvii.). To *Brain* he contributed articles on "Imperative Ideas" (vol. xviii., 1894) and on "Heredity and Neurosis" (vol. xx., 1897). The latter was his address as President of the Neurological Society. In the *Transactions of the Medical Society of London* (vol. xvii.) is a paper on "Some Neuroses of the Climacteric," with a summary of cases at Bethlem Hospital 1888–1903.

In 1907 he delivered the Bolingbroke Lecture on "The Factors of Insanity" before the South-West London Medical Society, and in the same year the Lumleian Lectures at the College of Physicians on "The Increase of Insanity." His conclusions were: "I do not find there is any real ground for alarm in the increased number among the insane; there are many reasons for the apparent increase." "It is noteworthy, too, that there is no increase in persons of the young and of the middle ages, the increase being greater after the age of sixty."

In 1909 he was Harveian Orator before the College of Physicians. He reviewed the treatment of the insane in

Harvey's day and the progress since, and referred to experimental psychology and hypnotism. As regards the latter he said: "Those mental disorders that are purely functional and such as do not cross the insane border-line may be benefited." In 1912 he received the honour of knighthood as a rather belated recognition of his remarkable career. Unfortunately he had had some years before this again to suffer a severe bereavement by the death of Mrs. Savage, who was thus unable to share in the honour conferred on him.

In 1912 also he was made the first President of the new Section of Psychiatry of the Royal Society of Medicine. In his address he gave a general review of the past, referring to the work of Crichton Browne at Wakefield, of Hack Tuke, Bevan Lewis, Wiglesworth and others. He spoke of Tuke's *Dictionary of Psychological Medicine* as a "mine still worth working," and said that in it would be found "many evidences that what seem to be quite new and original observations or beliefs are neither new nor original." Very characteristic of him are such remarks as the following: "Let us be collectors and recorders, but at the same time let us recognise that what seems to us to be fixed and established to-day may in the future prove to have been only partially true." "Agnosticism in science is not infidelity, and we must cultivate it." "We are prepared to follow truth where it leads, and a dim light is better than none in such darkness as the realms of life and consciousness." In 1912 he lectured to the Medical Graduates' College and Polyclinic on "Medico-legal Relationships of General Paralysis of the Insane" (*Lancet*, February 3, 1912).

During the late war he was one of the consultants attached to Lord Knutsford's group of hospitals for officers, and read a paper before the Medico-Psychological Association on July 27, 1916, on "Mental Disabilities for War Service." He also took part in the formation of the Enham Village Centres for Disabled Men. In July 1917 he wrote for our Journal on "Dr. Hughlings Jackson on Mental Disorders," summarising Jackson's well-known views as to the presence of positive and negative states in nervous and mental disorders. He also referred to his association with Jackson and Sutton in his early days at Guy's Hospital following the teaching of Gull and Wilks.

In addition to the numerous papers to medical journals already referred to, he wrote no less than twenty of the articles in Tuke's *Dictionary* and six in *Allbutt's System of Medicine* in the section of Mental Diseases (vol. viii.), perhaps the most important one being that on "General Paralysis of the Insane" in association with Dr. E. Goodall.

Enough has been said to show the comprehensive nature of his energies in connection with medical literature.

A short summary must be given of some other lines in which his vigour and inexhaustible vitality were displayed. In his earlier years at Bethlem Hospital his holidays were usually spent in walking tours with a friend, and in this way he visited Austria, the Tyrol and Norway, but Swiss mountaineering did not at first attract him. But, having won the Derby sweepstake at the St. Stephen's Club, he went to Zermatt, where he soon

"G. H. Savage as a Blasted Oak."
By Arthur Rackham, R.W.S.

became a vigorous climber. He made a record ascent of the Matterhorn, reaching the summit from the Hörnli in four hours. He once ascended the Weisshorn by moonlight, and his ascent of the Gabelhorn from the Trift Glacier is recorded in the *Alpine Journal*. He became a member of the Alpine Club, and was a friend of many well-known Alpine climbers, among whom may be mentioned Frederick Taylor, Howse, Clinton Dent and Makins. Eventually he became Vice-President of the Alpine Club.

For many years he was a member of the "Sunday Tramps," and was associated in this way with Leslie Stephen, James Sully and many others well known in the world of literature.

The Organon Club and the Casual Club also brought him into relation with many who became well known in science, such as Odling, Rolleston, Clifford Allbutt, Ray Lankester, Thistleton Dyer, Sprengel, Donkin, Balfour Browne and others.

He was a keen fencer, and the "Savage Shield," which he presented, is annually competed for at the Epée Club. He was a member of the Athenæum Club and of many dining clubs, such as the Sydenham, the St. Albans, the United Hospitals (Guy's and St. Thomas's), the Fifteen Club, and the College Club. He was a great raconteur and was always in request as an after-dinner speaker, his fund of information and humour being apparently inexhaustible. He was a most genial host. At Hurstbourne in Hampshire, where he had a cottage, he spent week-ends in fishing, cycling, golf and botany, enjoying every moment in association with his most intimate friend of many years, Seymour Sharkey.

In view of his botanical knowledge it was appropriate that he should have been for many years the representative of the College of Physicians on the Committee of Management of the Chelsea Physick Garden founded by Sir John Soane.

He was consulting physician to several private asylums, notably to the Priory, Roehampton, and Chiswick House, and also to the Earlswood Asylum, Redhill. He was also an Honorary Fellow of the Royal Academy of Medicine, Ireland.

For many months increasing ill-health had caused anxiety to his friends, but it was characteristic that he should fight against his disabilities. Gradually he had to abandon his more active pursuits, but still dined out as long as he was able. In May he retired from all official work, and only about three weeks before his death he expressed to the writer his conviction that he should not live beyond August. Shortly after this an attack of hemiplegia from which he did not regain consciousness mercifully relieved his sufferings, and he died on July 5, 1921.

By those who had been his colleagues he was always looked up to as a great master; he never lost interest in their careers, and many were the kindnesses to which those who worked with him can look back. He was always a ready adviser in troubles or difficulties. Many of his aphorisms remain in the memory, and his example of strenuous work and undying interest in his profession remains as a constant inspiration. Of him it may be truly said—"He being dead yet speaketh."

THE RESULTS OF TONSILLECTOMY IN ACUTE RHEUMATISM IN CHILDREN

By G. H. HUNT, M.D., Physician to Guy's Hospital and A. A. OSMAN, Medical Assistant, Guy's Hospital.

UNTIL ten years ago the practice of removing tonsils in cases of acute rheumatism, in the hope of preventing recurrences, was not often adopted at Guy's Hospital. During the last decade, however, tonsillectomy has been frequently done for this purpose, and as we have been unable to find statistics of any considerable number of cases showing the results of such treatment, we have attempted to follow up as many patients as possible to see how far operation influenced the liability to relapse.

METHOD OF INVESTIGATION

Letters were sent to about 250 patients, who had been in hospital for acute rheumatism, asking for information as to the frequency and nature of recurrences. In some of these the tonsils had been enucleated; in others no operation had been done. In most cases the questions were answered satisfactorily, but it soon became evident that a distinction would have to be drawn between vague limb and joint pains, occurring chiefly in damp weather, and definite recurrences of acute rheumatism. The plan was, therefore, adopted of restricting the term " recurrence " to those instances in which the illness was sufficiently severe to necessitate a return to bed for a fortnight or longer. We have only included those cases which, in the original illness and in the clinical history of the recurrence, were typical of acute rheumatism; cases of rheumatoid and other types of arthritis have been excluded. It is, of course, possible that some patients had recurrences of the infection, where the heart was attacked, but where the joint manifestations were so slight as to pass unnoticed; it is so difficult to get reliable evidence of this from the history alone that we have not attempted it.

While there are necessarily many possible fallacies in an investigation of this kind, we think that the figures presented are sufficiently trustworthy to be of some value. Where there seemed to be some doubt from the case report as to the existence of an organic heart lesion, the patient was re-examined.

Of some 250 cases investigated we have retained 144, as supplying reliable data. We have included only hospital patients in this series, and excluded those seen in private practice. The prognosis as regards recurrence is altogether different in the latter, for in these the conditions of feeding and housing are very much better. Moreover, they are able to convalesce in the country, a thing very difficult to arrange in the case of the hospital patient owing to the reluctance of the authorities in charge of convalescent homes to receive children whose hearts are or have been affected.

Results

The after-histories of 144 patients were analysed; enucleation of the tonsils was done in 66, and in 35 (53 per cent.) recurrences occurred. No operation was done in 78, and recurrences occurred in 33 (42 per cent.). Before drawing any conclusions from these figures, we think that at least three questions should be considered in both groups:

1. Is recurrence more likely after a second than after a first attack?

2. Does the presence of a heart lesion make the chance of a recurrence greater?

3. For how long were the patients traced?

1. *Is recurrence more likely after a second than after a first attack?*—Ninety-six patients were admitted to hospital for a first attack of acute rheumatism; recurrences occurred in 38 (40 per cent.). The tonsils were enucleated in 50 of these patients, and recurrences occurred in 23 (46 per cent.); no operation was done in 46, and recurrences occurred in 15 (33 per cent.). Forty-eight patients were admitted to hospital for a second or later attack; recurrences occurred in 30 (62·5 per cent.). The tonsils were enucleated in 16, and recurrences occurred in 12 (75 per cent.); no operation was done in 32, and recurrences occurred in 18 (56 per cent.).

It is clear from these figures that recurrence is more likely to occur after a second than after a first attack; the total number of cases—144 (96 + 48)—is sufficiently great for a difference of 22 per cent. (62 per cent. — 40 per cent.) to be significant. In both groups recurrence occurred more frequently in cases where tonsillectomy had been done, but the difference in relation to the total number in each group does not justify a positive conclusion that operation increases the liability to recurrence; the most that can be said is that the figures are suggestive.

2. *Does the presence of a heart lesion make the chance of a*

recurrence greater?—In the total 144 patients the heart was affected in 74, and in these 74 recurrences occurred in 39 (53 per cent.). In the remaining 70 recurrences occurred in 29 (41 per cent.). Here again the figures suggest that the presence of a heart lesion increases the liability to recurrence, but are not conclusive.

Table I shows the result of operation in patients with and without heart lesions after a first or later attack. The division of the patients into eight different categories necessarily makes the total number in certain groups inconveniently small; we have classified them in this way in the hopes that additions may subsequently be made from other sources. The figures, as far as they go, do not afford any evidence in favour of operation.

TABLE I

TOTAL CASES = 144 *Cases*

No Operation				Operation			
Heart affected		Heart normal		Heart affected		Heart normal	
Cases	Recurred	Cases	Recurred	Cases	Recurred	Cases	Recurred
33	15 (45%)	44	18 (41%)	40	24 (60%)	26	11 (42%)

First Attack = 96 *Cases*

No Operation				Operation			
Heart affected		Heart normal		Heart affected		Heart normal	
Cases	Recurred	Cases	Recurred	Cases	Recurred	Cases	Recurred
13	3 (24·5%)	33	12 (36%)	30	16 (53%)	20	7 (35%)

Second or *Later Attack* = 38 *Cases*

No Operation				Operation			
Heart affected		Heart normal		Heart affected		Heart normal	
Cases	Recurred	Cases	Recurred	Cases	Recurred	Cases	Recurred
21	12 (57%)	11	6 (55%)	10	8 (80%)	6	4 (67%)

3. *For how long were the patients traced?*—It is obvious that the time factor must be considered in any statistics of this kind. If a patient remains free from recurrences for, say, seven years, the fact is clearly more significant than if he remained free for only two years. Owing to the difficulty of fixing exactly the dates of first and subsequent attacks, we have only considered this factor in patients admitted to hospital in the first attack. These numbered 96, and Table II shows the frequency of recurrence after different intervals of time. The top horizontal line (in Roman numerals) shows the number of years during which the patient was traced, the lower line the number of patients who had recurrences. The vertical line shows the number of recurrences that occurred. Thus in the

patients whose tonsils were enucleated seven (marked *a*) in the Table) remained free from recurrence after being traced for two years, and two (marked *b* in the Table) had one recurrence within eight years of the first attack. The numbers are insufficient for any mathematical calculation of the chances of a recurrence occurring within a given number of years, but it is clear that, in patients not operated on, the chance of a recurrence within a given number of years is smaller than in those from whom the tonsils were removed.

TABLE II.

Operation Cases (43). *First attack*

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	No. of years traced.
No recurrence .	1	7(*a*)	0	8	1	6	2	0	0	1	Total = 26
1 recurrence .	1	1	1	0	0	0	0	2(*b*)	0	0	Total = 5
2 ,, .	0	1	1	0	1	1	0	0	0	0	Total = 4
3 ,, .	0	1	0	0	0	0	0	0	0	0	Total = 1
Occasional . .	0	4	1	1	0	0	1	0	0	0	Total = 7

Patients not operated on (42). *First attack*

	I.	II.	III.	IV.	V.	VI.	VII.	VIII.	IX.	X.	No. of years traced.
No recurrence .	0	8	5	7	3	4	6	0	0	0	Total = 33
1 recurrence .	1	2	0	0	0	0	0	0	0	0	Total = 3
2 ,, .	0	1	0	0	0	0	0	0	0	0	Total = 1
3 ,, .	2	0	0	0	0	0	0	0	0	0	Total = 2
Occasional . .	0	0	0	2	1	0	0	0	0	0	Total = 3

Summary and Conclusions

It will be seen from the above figures, and more clearly from the diagram, in which the number of recurrences is expressed as percentages, that enucleation of the tonsils is not a certain preventive of a recurrence of acute rheumatism; indeed in this series recurrences were more frequent in patients subjected to operation. It seems probable that, although the tonsils may be the primary focus of infection or portal of entry in the first attack, the infective agent may remain dormant in some other part of the body; the increased frequency of recurrence in patients with cardiac lesions suggests that the persisting focus of infection may sometimes be the heart itself, but this could only be established by a much larger series of figures than we have given.

As regards the advisability of tonsillectomy in rheumatic children, many considerations must influence the question. There may be local indications of tonsillar infection with enlargement of the neighbouring lymphatic glands; in such cases operation is probably advisable in order to prevent

further attacks of tonsillitis with consequent impairment of the child's general health, but our figures do not support the contention that operation in such cases diminishes the liability to

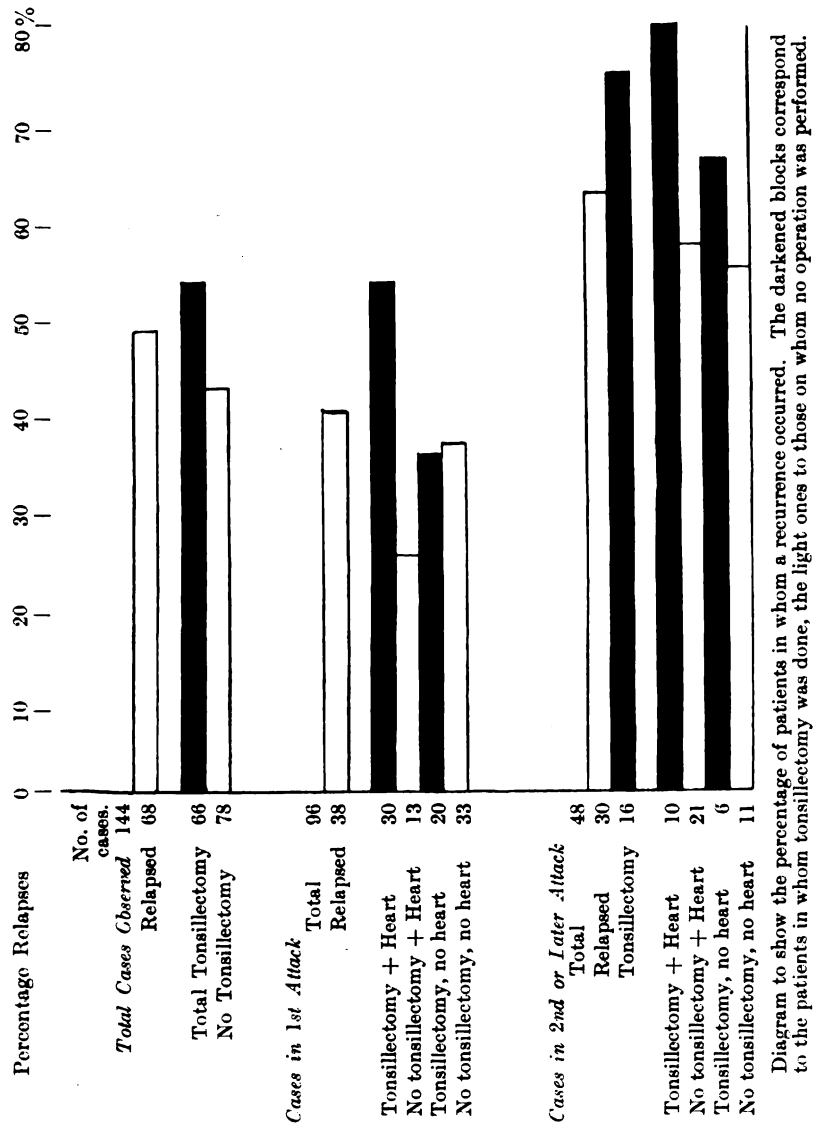

Diagram to show the percentage of patients in whom a recurrence occurred. The darkened blocks correspond to the patients in whom tonsillectomy was done, the light ones to those on whom no operation was performed.

rheumatic infection. It is perfectly clear that operation in rheumatic children whose tonsils and lymphatic glands appear healthy is quite unjustifiable; it is sometimes advised in such cases, and the practice cannot be too strongly condemned.

TONSILLAR AND RHEUMATIC INFECTIONS

By H. J. STARLING, M.D., Assistant Physician to the Norfolk and Norwich Hospital.

THE relationship between tonsillar and rheumatic infections has long been suspected and has often been affirmed.

Removal of the tonsils for the cure of rheumatic infection, at first by the guillotine and later by enucleation, has been both advocated and practised on a considerable scale. Nevertheless no definite conclusion as to the efficacy of this procedure seems to have been formed and observers differ greatly as to the value of the results obtained.

It seems worth while, therefore, to record some clinical experience of rheumatic infections during a period of nearly four years.

While working at the Military Heart Hospital at Colchester during the war, I was very impressed with the frequent history of tonsillitis, both with and without rheumatism, in the various types of cardiovascular disease which were received there. My American colleagues seemed convinced of the essential relation between tonsillar and rheumatic infections to a much greater degree than were my compatriots, and the American textbooks on heart disease also give more prominence to this question than do the British.

Since May 1919 up to the present date I have kept as accurate a record as possible of the occurrence of tonsillar infection in cardiovascular disease, and the results are compiled in the tables at the end of this paper. Table I (p. 404) shows the cases in which the tonsillar infection was noted, and Table II (p. 405) the cases on which enucleation was performed.

These tables show how great a proportion of the cases had tonsillar infection, both remote and present. The figures, however, do not, by any means, represent the full incidence. It has been my repeated experience to note the transient infection of the tonsils in cases which do not at other times show direct evidence of it.

Quite recently a case of rheumatoid arthritis was admitted into the Norfolk and Norwich Hospital under Dr. Burton-Fanning, who asked Mr. Carruthers and myself to report on the condition of the tonsils. Neither of us could discover any

enlargement of the glands under the lower jaw, nor was there any evidence of infection to be seen in the tonsils, which were not enlarged, the left one being a little ragged. The patient remained in hospital some weeks, and ultimately Dr. Burton-Fanning asked me to see her again. On this occasion the left tonsil was obviously protruding into the throat, and on pressure it was seen to be a mere bagful of pus.

Usually when there has been definite tonsillar infection, the glands under the angle and ramus of the lower jaw are notably enlarged. This, in my opinion, is a more sure sign of tonsillar infection than the appearance of the tonsil itself. These glands are often present when no pus can be squeezed out of the tonsil, although occasionally the reverse condition is present. Hence in the tables, + represents the presence of enlarged lymph glands, ++ obviously enlarged and infected tonsils, +++ huge tonsils. In this last category, enlarged lymph glands are usually present, but in a few cases they have been notably absent.

Similarly the figures relating to a past history of sore throat do not represent the full incidence. Nothing is more striking than the forgetfulness of patients in regard to this incidence of infection. A sore throat or definite tonsillitis appears so small a matter to some people that it is easily forgotten and is only recalled by a parent or friend.

The figures in this respect, therefore, denote severe tonsillitis or quinsy, or are cases which have been actually observed in hospital and a note made of a symptom which the patient considered trivial in relation to his general disability.

In Table I the incidence of tonsillar infection may be summarised as follows:

Under 30 years of age, 33 cases, mitral or aortic or combined.

Tonsils +++10 cases = 30·3 per cent.
++13 cases = 39·2 ,,
+ 2 cases = 6·06 ,,

(A history of sore throat was noted in 6 of the above cases.)

History of sore throat alone 2 cases = 6·06 per cent.

Total incidence of tonsillar infection = 81·62 ,,

No history or evidence of tonsillar infection,
6 cases = 18·2 per cent.

To this age class there should be added:

Pericarditis, 1 case with no other rheumatic infection except tonsillitis and huge tonsils.

Subacute infective endocarditis, 1 case, following chorea and rheumatism, and preceded and accompanied by sore throat and big tonsils.

Ages of 30 years and over, 31 cases, mitral or aortic or combined.

+++	7 cases	= 22·6 per cent.
++	7 cases	= 22·6 ,,
+	1 case	= 3·22 ,,

(A history of sore throat in 12 of the above cases.)
History of sore throat only 4 cases = 12·88 per cent.
Total incidence of tonsillar infection = 61·3 ,,
No history or evidence of tonsillar infection,
12 cases = 38·7 per cent.

As would be expected, the incidence of tonsillar infection in cases under 30 years of age (81·62 per cent.) is considerably above that of 30 years old and upwards (61·3 per cent.).

St. Laurence [1] in a paper on this subject gives the following figures: 94 children, of whom 58 had organic heart disease, 49 boys and 45 girls. Ages from 4–16 years, average age 8½ years.

Tonsils markedly enlarged	in 12 cases = 13 per cent.
Moderately enlarged Protruding Buried	in 65 cases = 69 ,,
Not enlarged	in 17 cases = 18 ,,

The tonsillar lymph nodes behind the angle of the jaw were palpable in 100 per cent. of these cases before operation.

Indications for operation are given as:

(1) Hypertrophy of the tonsils, whether protruding or buried.
(2) Evidence of infection.
(3) Enlargement of tonsillar lymph nodes, regardless of the size and appearance of the tonsils, and likewise
(4) Whenever the tonsils are known to be infected.

This paper only came to my notice some six months ago and the recommendations contained therein summarise very completely the conclusions I had already formed.

My figures differ from those of this writer, insomuch as I have only included cases of definite organic heart disease, representing a later period and progress of infection, and I have excluded cases with systolic bruits only.

From my observation of these cases of rheumatic heart disease, I have been forced to the conviction that tonsillar infection is the chief portal for rheumatic infection, and also,

although to a lesser degree, the chief source of infection in such cases.

In Norfolk the severe form of rheumatic fever is almost unknown; at the worst it consists of multiple arthritis and pyrexia, the joints being red, swollen and tender, but not to any marked degree; usually the attack consists of fleeting pain or swelling of one or more joints with a few days' pyrexia. Nevertheless endocarditis is fairly common, and it is possible that the primary infection is more noticeable in this neighbourhood than in other districts in which severe arthritis masks the minor symptoms.

The following cases, 4 in number, not included in the tables, appear to show that tonsillar infection was the prime origin of the subsequent rheumatic infection, and also was responsible for the long period of pyrexia which occurred in each case.

Case A.—Male, aged 17. Seen on May 24, 1920. Four years previously he had had a severe cough, and was told by the school doctor that his heart was dilated and was forbidden all games for two terms. After this he apparently made a complete recovery, went to a big public school and played Rugby football and all other games with distinction. During the Easter holidays of 1920 he developed a sore throat, with some impetigo of the face, which lasted one week. A few days later he was seen by Dr. Aldred for a recurrence of the sore throat, malaise and pyrexia, and within the next week a systolic apical murmur and pericardial rub were heard. On May 24 his face was markedly pale, the heart was not enlarged, but a loud systolic blow could be heard at the apex in all postures and phases of respiration. The right tonsil was large, boggy, and inflamed, the left was slightly enlarged and red and there were enlarged glands under the jaw on both sides There had been a mild pyrexia (up to 100°) for the previous fourteen days. Immediate tonsillectomy was advised but postponed. He then developed pain and redness of the knees, ankles and wrists and the pyrexia continued. On June 20 a very early but definite diastolic blow could be heard at the 3rd left intercostal space close to the sternum. On June 22, the pyrexia still continuing, the tonsils were enucleated by Mr. E. W. Everett. Within the subsequent twenty-four hours the temperature rose to 102°, but twelve hours later fell to normal and remained so during the convalescence. Within one week his pallor had completely disappeared, he began to put on weight and he went home two to three weeks after the operation. On his discharge from the nursing home, the diastolic blow was very marked. He returned to school in October 1920, not being allowed to take any form of exertion apart from his work. I saw him again in September 1921. He looked fit

and well, and had just finished a long motor-bicycle tour. The apex beat was in the 5th space, in the nipple line, the loud, blowing apical systolic bruit was unaltered, but the diastolic blow was only perceptible with the utmost auditory concentration. At the present date he has had no recurrence of any disability and is able to lead an active though not a strenuous life.

Case B.—Male, aged 6, sent to my Out-patients on March 6, 1920. He had never been a strong child, but in the summer of 1919 he began to have attacks of fever and sweating, which lasted some weeks at a time. He was a very thin, ill-looking child, with marked facial pallor. The heart was enlarged and there was heard at the apex a loud systolic bruit with a low hum in diastole. The pulse rate was 94 with frequent ventricular extrasystoles. He was admitted at once. The tonsils did not appear to be enlarged and the glands under the jaw were only slightly enlarged. As the pyrexia did not abate the tonsils were removed on April 20, 1920. The chart shows the temperature before and after the operation. The child was discharged on May 20, and made marked progress during the next two years; colour, activity and growth were all excellent. Towards the end of 1922 he was noticed to be relapsing, the pallor returned and activity diminished. The tonsils could be seen, there were many enlarged glands and some muco-pus in the nasopharynx. He was readmitted on January 25, 1923; the tonsils, which were found to be deeply embedded and each as large as a small cherry, were enucleated. Previous to his operation he had had several rises of temperature, but this remained normal until his discharge. When last seen in April he seemed to be regaining his former improvement.*

Case C.—Female, aged 18. In June 1921 she had tonsillitis and was just recovering from this when she had an attack of rheumatic fever with pyrexia, for which she was in bed six weeks. She recovered from this except for slight morning stiffness and was all right until November. In this month the stiffness and swelling of the joints and fever returned, and she was unable to stand or to use her hands. Her temperature remained high until December 12, 1921, when she was sent into hospital.

She was a tall, pale girl, the tonsils were enlarged, very red and full of pus, and there were many enlarged glands. The heart was not enlarged and no bruits could be heard. There was much swelling of the wrists and ankle-joints, which were immovable. The finger-joints were "saddle-shaped" and swollen. The pyrexia continued till December 30, when her tonsils were enucleated.

After the operation the pyrexia ceased and her general condition and colour were much improved, but there was no change in the joints. An autogenous vaccine was made from streptococci cultured from her urine, but after six injections very little improvement was noted.

* See Temperature Chart on p. 406.

March 10, 1922, 10 c.c. of 5 per cent. peptone (Martindale) was given intravenously and repeated every four days. By March 24 considerable improvement had taken place in all the joints and the patient could walk and knit. Twelve peptone injections were given and she was discharged on April 11, 1922; her colour and general appearance were very good.

She attended Out-patients, and some six months later developed an acute gingivitis, pyorrhœa and recurrence of joint trouble, but there was no pyrexia. Dr. Claridge cultured a streptococcus from the gums and a vaccine was made from this which she has been given since. At the present date she is greatly improved, looks fit and well, has grown considerably, can walk some miles, can kneel down and use her hands normally.*

Case D.—Female, aged 16, seen on October 19, 1922. Three years previously she had a severe attack of rheumatic fever; " the heart was not affected."

The tonsils were enucleated in the following year. One year later she had " congestion of the lungs." In spite of these illnesses she had been very fit, and played all games at a big school for girls. Early in September 1922 she had a mild attack of scarlet fever, but her temperature did not come down to normal for three weeks. After one week of normal temperature she was allowed to get up. On October 11 she developed fusiform swelling and redness with pain in the proximal interphalangeal finger-joints, with some swelling of both ankles. The temperature is shown on the chart.

Her symptoms developed as follows:

October 19.—Complete dullness on percussion, with bronchophony and tubular breathing over the right base. A pericardial rub over the 3rd right intercostal space. Tonsillar stumps could be seen, highly inflamed and exuding pus.

October 24.—Large pericardial effusion. Some dullness and tubular breathing over the left base. Right chest aspirated, 8 oz. fluid removed, which contained some blood and a few white cells. Finger-joints less swollen.

October 28.—Dullness of left base much increased, left chest aspirated, no fluid obtained.

November 1.—Pericardial dullness nearly disappeared, pleural effusions unaltered. Fingers and ankles again swollen.

November 8.—Slight twitching of fingers and limbs. Systolic apical bruit present. Apex beat behind 6th rib in the nipple line.

November 11.—Severe chorea, grimacing of face, limbs jerking violently. Apex beat outside nipple line in 6th space, systolic apical bruit much louder. Further arthritis. Tonsillectomy advised.

November 13.—Operation performed by Mr. Carruthers. Tonsillar stumps removed; many bleeding points had to be tied. The patient stood the operation well.

* See Temperature Chart on p. 407.

November 30.—Her doctor reported that the chorea ceased with the operation, and that all the arthritis had disappeared, but the patient had been quite irresponsible, weeps easily and will not answer questions. She sleeps and eats well.

I saw the patient again on January 7, 1923. Her chest had quite cleared up. The apex beat was in the 5th space, just outside the nipple line, and a systolic apical bruit was the only one to be heard. She was still somewhat lachrymose.

In *April* 1923 her physique and appearance were vigorous and her mentality normal. The apex beat was in the 5th space in the nipple line, but it was heaving quietly, as were the carotids. At the 3rd left intercostal space could be heard a short, distant diastolic blow accompanying an accentuated second sound.

In each one of these cases the pyrexia had lasted for weeks or months and showed no signs of abatement before the operation, after which the pyrexia either ceased abruptly or began a gradual descent to normal.*

Before discussing the cases in which enucleation was performed, it seems advisable to give some details in regard to the signs by which improvement or otherwise is estimated, and some digression is thereby involved. The textbook descriptions of the signs of aortic regurgitation appear to me to be misleading in reference to the early stages of this lesion. An early aortic lesion should be suspected in every patient who complains of or shows signs of effort intolerance in conjunction with a slow pulse. The patient should be examined in three postures—standing, lying on the back, and lying on the left side. He should be instructed to take a deep breath and then expire as completely as possible, letting the chest wall sink to its fullest extent. Then while the patient is holding the breath in expiration, auscultation should be made at the 3rd left intercostal space close to the sternum. In these early cases the aortic second sound will be clear, sometimes accentuated, but it is accompanied by a faint whiff, which is best imitated by letting the breath out between the lips held in a whistling position. I have been able to help many other observers to hear this faint but clear sound, which is comparable to the fine tubular breathing of a distant patch of pneumonic consolidation, by instructing them to relax their auditory attention for near sounds and to listen only for distant sounds. The effort is very similar to the abolition of accommodation for near objects, employed when looking at the fundus oculi by the direct method. These cases of early aortic regurgitation show no other abnormal cardiovascular sign. The

* See Temperature Chart on p. 408.

blood pressure is normal, the heart is not enlarged, but the pulse rate is usually slow. Such early lesions are almost impossible to detect in the presence of a high pulse rate, and a definite diagnosis must then be postponed until the rate of the heart diminishes. These early lesions I believe to be much more common than is suspected.

From the date on which a bruit is first heard, its development is fairly rapid, so that in a period of one to three months the leak becomes audible to the average observer and progresses until it occupies an appreciable period of diastole. Only at a later period are manifested the other clinical signs in the pulse, blood pressure and enlarged heart. A systolic blow is also added and the aortic disease becomes frank in type.

A small percentage of the aortic cases under my care have become practically stationary even after they have become frank in character. In these I have noticed the onset of a harsh type of systolic murmur, maximal at the 2nd right intercostal space. As time progresses, the harsh blow changes to a rumble, comparable to that typical of the apical murmur of mitral stenosis, and there is no doubt that aortic stenosis is taking place. In my opinion this is the most favourable development in aortic cases.

In a few cases, and in these only after tonsillectomy, the diastolic blow has become so modified as to be nearly but never completely inaudible. After the period of primary infection has passed, cases with valvular lesions should not show any pallor. If pallor is present, some form of infection is present also. It is taught that pallor is one of the signs of aortic regurgitation, but I believe this to be incorrect.

Of a series of 35 cases of aortic regurgitation (without mitral stenosis) 24 are noted as having a good colour and the remainder as having a fair or pale colour. The association of pallor with aortic disease probably arose from its frequently syphilitic origin in adults, the specific treatment for which either had not been given or was incomplete.

In the cases of mitral stenosis the degree of the lesion is estimated by the character of the diastolic rumble at the apex.

Degree 1.—A very short presystolic "clip" can be heard only when lying on the left side with or without previous exercise.

Degree 2.—A short presystolic rumble can just be heard when the patient is upstanding, and is quite definite when he lies on his back.

Degree 3.—A well-marked presystolic rumble heard in all postures.

Degree 4.—The rumble occupies the whole of a long diastole in every posture.

Apart from physical signs such as bruits, enlargement and pallor, the severity of each heart case must be estimated by the effort tolerance. Improvement in physical efficiency is a direct guide to the value of treatment and is the chief test on which one relies, especially in cases of early mitral stenosis, the progress or retrogression of which it is difficult to determine by the auditory phenomenon alone.

Many cases are subject to recurrent, though mild, attacks of rheumatism, sore throats, or frequent colds. Each of these minor infections is a serious menace to the already damaged endocardium, and often gives rise to fresh endocarditis.

Cases in which enucleation was performed are shown in Table II.

Of these 86 cases there were :

Aortic regurgitation	7 cases.
Mitral stenosis with aortic regurgitation	3 cases.
Mitral stenosis	23 cases.
Pericarditis	1 case.
Enlarged heart, one with adherent pericardium	2 cases.

The ages varied from 6 to 44, the average being 17 years.

The tonsillar condition is recorded as follows :

+++ 2 cases =	5·5 per cent.
++27 cases =	75 ,,
+ 7 cases =	19·5 ,,

and tonsillitis is noted in addition in 10 of the above cases.

The results were as follows :

1. No improvement at all	7
2. Stationary	1
3. Improvement	13
4. Marked Improvement	13
5. No further record	2

By reference to the table, it will be seen that the operation was done both for early and advanced cases and also for mild as well as acute infections. No case appeared to be in any way the worse for the operation, even those whose lesions were advanced or whose infection was acute. I have been very conservative in my estimate of results, so that improvement means a very considerable change for the better in physical efficiency; and marked improvement implies that the cases

were almost new people in their acquisition of health and strength. Even the improved cases were able to resume work which they had had to give up.

Examples of each result are given briefly.

1. *No benefit.*—No. 33, a pensioner, 44 years old, chronic rheumatism for many years and greatly enlarged heart. Rheumatism recurred soon after the operation, and he is not able to return to work.

No. 81. A child of 8, taken ill with sore throat and enlarged glands on November 11, 1920, with high fever. On December 5 pericarditis. Salicylates had no influence on the temperature. December 14 tonsils enucleated. Temperature fell for forty-eight hours and then rose again. On January 1, 1921, bronchopneumonia. Death on February 15. Autopsy showed pericardium densely adherent all over the anterior surface of the heart; much recent lymph.

2. *Stationary.*—No. 43. Male, aged 24, no progression, nor retrogression of lesion twelve months after operation. The stump of the left tonsil was still present.

3. *Improved.*—No. 85. Boy, aged 14. Admitted October 8, 1921, for dyspnœa, malaise, and aortic regurgitation. Some fever after admission. Operation October 14, 1921. The boy is known to be fit and well and doing full work in London as a page-boy.

No. 86. Male, aged 33. Heart much enlarged, apex beat 6th space, 6″ to left of M.S.L. Definite indrawing of 4th–6th intercostal spaces with ventricular systole. Chief complaint, severe tachycardia which has kept him from his work since 1917. Operation on March 10, 1921. Seen last in February 1923. Doing full work as a shunter. Physique and colour good. Apex beat in 6th space, 5″ to left of M.S.L.

4. *Marked Improvement.*—No. 35. Male, aged 24. Under observation from June 1919 to November 1920 for tachycardia and severe precordial pain, unable to do any work, very pale. An early diastolic blow heard first in August 1920. Operation November 1920. Seen in February 1923. He was working at a butcher's shop, cycling five miles there and back. His heart was not enlarged and the diastolic bruit was very short and high-pitched. Colour very good.

No. 78. Male, aged 19. Under observation for dyspnœa and tachycardia since 1919, very pale, heart not enlarged, increasing diastolic blow. Operation June 1921. Seen in February, colour good, physique big. Can walk five miles quite well. Heart not enlarged, a distant but very short diastolic blow can just be heard at the 2nd right intercostal space. B.P. 140/84. P.R. 72.

No. 133. Female, aged 8. A year previously was in Jenny Lind Hospital for chorea for eight weeks. In March 1922 chorea began again. Admitted to hospital March 19, 1922, general choreic movements. Erythema nodosum on left elbow.

Loud systolic and short presystolic murmurs at apex. Operation March 28. Chorea much diminished very soon afterwards; discharged to Convalescent Home April 21, 1922. Seen again in March 1923. Has had no further trouble. Systolic bruit has disappeared; a short presystolic clip can be heard at the apex only after exercise.

I have not included in my tables a number of children and young adults whom I have seen for functional disorders of the heart. The nature of this disability, the same as the D.A.H. of the army, is still a matter of dispute. It may be defined as an inherent instability of the nervous centres, the symptoms of which are often manifested or aggravated by minor infections.

In the majority of these cases tonsillar infection is present, and I regard enucleation of the tonsils as a most valuable means for the cure or alleviation of the condition. In only a few cases was there any previous history of rheumatic infection. A further period of time is necessary before any conclusion can be made as to the efficiency of the operation in preventing rheumatism or a relapse of the original disability.

Effect on Chorea

I have mentioned one case (Case D) in which the chorea disappeared with the operation for tonsillectomy, and the same result occurred in two others of this series. In other cases although the choreiform movements were not abolished, yet they were notably diminished. Further, the mental condition of the patients was so improved that screens round the bed were no longer thought necessary and, by means of massage and passive movements, muscular co-ordination was soon restored.

In only one of the 9 cases who had chorea, either before or at the time of the operation, did a relapse occur. This was in No. 11 of Table II. The operation was done in September 1920 and the child grew and improved very markedly. She was brought to my Out-patients in April 1923 for slight twitching of the left hand. This was not sufficient to make her give up her work as a nursemaid. Her age was then 15 years, and her menstrual periods began in February, a process which may have had some agency in the return of the chorea.

Effect on Other Rheumatic Infections

Except for Cases 33 and 66 of Table II, no one of these cases has reported again for rheumatism in any form. The period of observation, four years for the lowest numbers to

six months for the highest numbers, is not sufficiently long, in some of the cases, to draw any definite conclusions as to the value of this operation in preventing rheumatic recurrence.

St. Laurence,[1] however, gives some valuable statistics on this point. In the summary of his paper he records:

(1) Eighty-five children, some with several previous rheumatic manifestations before operation, were observed for a period of three and a half years after operation.

(2) Recurrent inflammation of the tonsils occurred in 73 per cent. of the cases before operation, and only 7 per cent. of these afterwards.

(3) Tonsillar lymph nodes were palpable in 100 per cent. of these cases before operation; after operation they were not palpable in 59 per cent., palpable though smaller in 41 per cent.

(4) One or more attacks of chorea in 43 of the cases before operation, afterwards no recurrence in 35 of these cases, or 84 per cent.

(5) One or more attacks of chorea in 40 cases before operation, no recurrence in 20 per cent. of these cases afterwards, or 50 per cent.

(6) Six cases showed myositis, or bone or joint pains, before operation, no recurrence in 47 of these cases afterwards, or 77 per cent.

F. J. Poynton, in his most instructive paper[2] on an epidemic of acute rheumatism in children, occurring from July 1919 to June 1920, gives the following data:

(1) Acute tonsillitis may be followed at once by severe and even fatal rheumatism.

(2) Guillotining of the tonsils when inflamed may be followed at once by an attack of rheumatism.

(3) Unhealthy conditions of the throat are very frequent in the rheumatic child. Thus, in 172 cases of rheumatism there were 22 examples of rheumatism following immediately on an attack of tonsillitis, and 38 with enlarged and unhealthy tonsils.

He states that "enucleation, though a valuable operation in many cases, does not prevent further attacks. In the above series there were 17 examples of rheumatism occurring after enucleation, the operation varying in time from just before an attack to five years previously."

For enucleation to be a specific prevention or cure of rheumatism would be an amazing clinical phenomenon, and we are not justified in expecting such results from it.

The evidence of tonsillar infection is principally in the presence of enlarged lymph glands. St. Laurence's figures show

that these glands could not be felt in 59 per cent. of the cases after operation, and even this does not denote an entire clearance of infection, whereas the glands, although smaller, remained present in 41 per cent. of the cases.

Further, as long ago as 1911, F. J. Poynton [3] wrote on the occasional association of rheumatic infection with appendicitis. I have recently seen one case of severe appendicular colic necessitating the removal of an inflamed appendix following directly after an acute tonsillitis; another case of chorea which developed within one month of discharge from hospital after an operation for appendicitis; and another case of chorea of two months' standing with severe abdominal colic for two weeks, which cleared up within a few days after tonsillectomy. All these three cases had enlarged tonsils and glands. The lymphatic infection in these cases was obviously not confined to the tonsils and adjacent glands. The spread of infection into the lymphatic glands is the probable explanation of some of the failures of tonsillectomy.

Case C, to which I have referred at length, is now a typical case of rheumatoid arthritis, although in her primary attack the nature of her arthritis could not be differentiated from an acute rheumatism. Similarly Case D, despite a previous attack diagnosed as acute rheumatism, in the last illness showed an arthritis which was rheumatoid and not rheumatic, if such terms may be used for differentiation. Yet the patient has now a definite endocardial lesion.

A prolific vaccine therapy, based on the bacterial content of the fæces and urine, is and has been extensively employed for the treatment of chronic rheumatism and rheumatoid conditions. These conditions, as well as acute rheumatism, have a frequent origin in tonsillar infection, and it would seem that the ultimate type of the rheumatic infection is determined principally by the habitat of the infecting streptococcus.

Rheumatic fever and chorea would seem to be derived from tonsillar infection passing into the blood stream, whereas the rheumatoid conditions are frequently dependent on a similar infection commencing in the tonsils, which has taken up its focus in some part of the alimentary tract. In the latter type, dental infection is also common, probably through the same channel.

Rheumatic infection greatly depends on conditions of soil and climate, as is shown by its definite geographical distribution. Providing that a child returns to the same environment as that in which it first contracted the rheumatism, it is not surprising that relapses occur despite the benefits of enucleation.

There is not the slightest doubt that air and sunshine have an immense effect on the cure of rheumatic conditions. The full benefits of enucleation will not be obtained until children with rheumatic infections can be raised to a high level of resistance and of general nutrition by after-care in the country, where treatment by heliotherapy can be employed to its fullest extent.

Dangers of the Operation

Barker, in his Clinical lectures at the Johns Hopkins Hospital,[4] insists on the removal of enlarged tonsils in most cases of rheumatic heart disease, and states that this should be done between but not during the attacks, since there is danger of throwing more cocci into the blood. I have already quoted Poynton's cases of rheumatism following directly after the guillotining of the tonsils. In only one of my own series have I seen any ill effects as the result of the operation, and in this fibrillation ensued within fourteen days after the operation—Case 19, Table II.

But in view of Dr. Barker's remarks the following cases may be discussed:

Table II, Case 134. Male, aged 13. Admitted to hospital June 8, 1922. He had had pneumonia at three years, scarlet fever at six years. He could never run fast because of shortness of breath. One month previously he had had growing pains in the legs. He was a spare, very pallid child. The heart was not enlarged; a presystolic and systolic murmur could be heard at the apex, and a systolic and harsh diastolic blow at the 2nd right intercostal space. Pulse rate 130, temperature 100. The temperature came down to normal in three days, and remained there for four days. Then he had a temperature of 100 every night until June 28, when the tonsils were removed. On July 16 the tip of the spleen was palpable for the first time, and by October 14 was distinctly larger. He had had periods of mild pyrexia which ceased after September 20. But from July 16 he was placed on the balcony, and from this date his weight increased and his pallor disappeared. On November 8 he was discharged to the convalescent home, looking well and having put on one stone in weight since his admission. On his return from Cromer, his father sent a motor to meet him, but the boy missed this and started to walk all the way home. He had walked some five miles when the motor overtook him and brought him back to the hospital. He was not in the least tired with his exertion and his pulse rate was 80.

He was seen at Out-patients at the end of April of this year. He has grown big and strong, and looks the picture of health. The tip of his spleen is just palpable, the bruits are not changed except that the systolic bruit in the aortic area is very harsh.

It may be thought that the operation liberated fresh bacterial infection which settled on the already damaged valves, giving rise to a splenic infarct. If this was so, the infection must be healed, as I have not yet seen a case of subacute infective endocarditis whose colour and weight improved so greatly and continuously as has this case.

Case D may be thought to have had the aortic valves infected as the result of tonsillectomy. It would be equally valid to hold that the mitral valves were already infected before the operation and that the infection spread later on to the aortic valves.*

It is a moot point, therefore, when tonsillectomy, if decided upon, should be performed. I think it is sound to regard and to treat the tonsils in much the same way as the appendix is treated.

Tonsillectomy should be performed, if possible, after the acute infection has subsided. But it must be remembered that the longer the infection proceeds, the more extensive the results. Hence, as with appendicitis, if the inflammation does not subside speedily, the infected organ should be removed.

In apyrexial attacks of chorea and rheumatism, tonsillectomy should be done at the earliest possible moment. It is obvious that the earlier the operation is performed in cases of rheumatic infection, the more striking is the benefit. In my series are several quite old-standing cases of mitral stenosis and aortic regurgitation who derived much benefit from the operation. These cases, however, were definitely chronic and the operation was done in a quiescent interval.

Cases of advanced valvular disease who are so bad as to require rest will not, in my small experience, derive much benefit, although it is often obvious that their disability is increased by the chronic tonsillar infection. It might be well to try some other method, such as diathermy, for the alleviation of these cases.

In my opinion enucleation of the tonsils should be regarded as a serious operation necessitating the same precautions as other major operations. It is far better performed on an In-patient rather than in the Out-patient department. This is not possible in the case of many children at a hospital, but should be regarded as essential in adults, in whom the operation is far more severe.

* Both these cases were seen again in August 1923. Case 134 has so increased in physique and general fitness, that he is going to take up light gardening as an employment.

Case D is so well that she is to be allowed to return to school in September of this year. The diastolic murmur in the aortic area, after having been frankly audible, can now only be heard with difficulty. She has regained her former weight and colour.

I feel somewhat diffident in presenting these conclusions from so comparatively small a number of cases, but they have the advantage of being closely observed. I have to express my grateful thanks to my colleagues in the Throat Department of the Norfolk and Norwich Hospital, Messrs. Everett and Carruthers, for all the work they have done on my behalf. My gratitude is due to Dr. Burton-Fanning for his generous loan of beds, without which I should have been unable to observe these cases as in-patients. I am also greatly indebted to the Medical Research Council for a grant which enabled me to pursue these investigations.

Summary

1. The tonsils are the main portal and focus of rheumatic infection.

2. The presence of enlarged lymphatic glands under the jaw is a more constant proof of tonsillar infection than the appearance of the tonsils themselves.

3. Tonsillar infection not only initiates the onset of rheumatic conditions, but may directly prolong an acute attack or be the cause of subsequent and repeated attacks.

4. Enucleation of the tonsils is, therefore, a most valuable means by which the acute attack may be ended and further infection prevented.

5. In order to be effective every particle of tonsillar tissue should be removed. A mere tag or stump left behind may be as potent a source of infection as were the whole tonsils before removal.

6. In the course of rheumatic infection the earlier the tonsils are removed the greater is the benefit derived.

7. The benefits of the operation are manifested not only in the acquisition of a healthy colour, an increase in weight and physical efficiency, but also in the prevention of further infection of the endocardium, and an apparent mitigation of the damage already suffered by it. The operation also effects the removal of an infective focus, the toxin from which is prejudicial to the heart muscle as well as to the whole system.

8. After the operation, the patient, whenever possible, should be placed in an environment of open air and sunshine, in order that his general nutrition may be raised to the highest level.

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[2] F. J. Poynton: *Lancet*, 1920, ii. 1086.
[3] F. J. Poynton: *Researches on Rheumatism*, pp. 359 *et seq.*, 1913.
[4] L. F. Barker, quoted by A. D. Hirschfelder: *Diseases of Heart and Aorta*, p. 417, 1910.

TABLE I.

Aortic Regurgitation.									*Mitral Stenosis.*							
Number.	Age.	Rheumatic Fever.	Chorea.	Tonsillitis.	Enlarged Tonsils.	Colour.	Progress.	Mitral Stenosis.	Number.	Age.	Rheumatic Fever.	Chorea.	Tonsillitis.	Enlarged Tonsils.	Colour.	Progress.
15	38	—	—		++	Good	S.	+	6	22	1	1	+	++	Pale	S.
27	17	3	—	+	++	,,	P. +	+	8	34	1	—	—	+	Good	?
37	21	1	—	—	++	,,	P. +	—	10	19	2	—	—	+++	,,	I.
56	20	1	—	—	++	,,	P.	—	14	32	—	1	+	+++	,,	P.
57	35	—	—	—	—	,,	S.	—	17	17	1	—	—	++	,,	I.
58	23	1	—	—	—	,,	S.	—	21	27	1	—	+	+	Pale	P.
60	29	1	—	—	+++	,,	P.	—	24	27	—	3	+	+	Good	P. +
62	19	1	—	—	+++	Pale	P +	—	30	21	—	—	++	—	Pale	P.
63	27	1	—	—	++	,,	P.	+	39	31	—	—	+	++	,,	S.
64	20	1	—	—	—	,,	P.	+	42	25	—	—	—	+++	Good	P.
65	45	—	—	—	++	,,	P.	+	45	2	1	—	—	+++	Pale	P. +
67	24	1	—	—	++	Good	P.	—	47	22	1	—	—	+++	Good	S.
68	38	—	—	—	—	,,	S.	—	53	24	1	—	+	+++	,,	P.
75	27	1	—	—	—	,,	S.	—	71	20	1	—	+	++	,,	P.
82	24	2	—	+	++	Pale	P.	+	73	34	—	—	—	—	,,	P.
84	31	1	—	++	—	Good	S.	—	76	16	—	1	—	++	Pale	?
87	36	1	—	++	—	Pale	P.	—	79	36	—	—	—	—	,,	S.
88	45	—	—	—	+++	Good	P.	—	83	28	2	—	—	—	Good	P.
89	52	5	—	—	++	Pale	P.	—	90	44	1	—	—	—	,,	?
95	34	—	—	—	+++	Good	S.	+	91	31	2	—	+	++	Pale	P.

TABLE II.—*Tonsils Enucleated.*

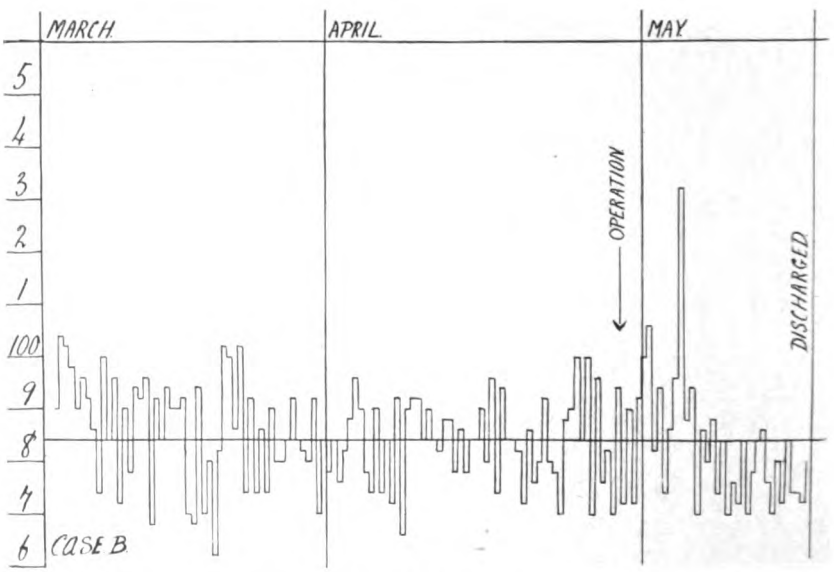
Aortic Regurgitation.										*Mitral Stenosis.*									
Number.	Age.	Rheumatic Fever.	Chorea.	Tonsillitis.	Enlarged Tonsils.	Colour before Op.	Colour after Op.	Progress.	Mitral Stenosis, Degree of.	Number.	Age.	Rheumatic Fever.	Chorea.	Tonsillitis.	Enlarged Tonsils.	Colour before Op.	Colour after Op.	Progress.	Degree of Stenosis.
12	16	2	—	—	+++	G.	G.	P.	—	1	11	1	—	—	+	P.	G.	I.	1
19	12	1	—	+	++	G.	G.	P.	2	3	18	5	—	—	++	P.	P.	P.	4
35	24	2	—	—	++	G.	G.	M.I.	—	11	12	—	1	—	++	P.	G.	M.I.	1
43	24	—	—	—	++	G.	G.	S.	—	13	37	1	—	—	+	G.	G.	I.	4
69	23	—	—	—	++	P.	G.	I.	—	18	7	1	—	—	++	P.	G.	M.I.	1
78	19	1	—	—	++	P.	G.	M.I.	—	23	6	—	—	+	+	P.	G.	M.I.	1
86	33	—	—	—	++	P.	G.	I.	—	25	32	1	—	—	++	G.	G.	M.I.	1
97	11	—	1	+	+	P.	G.	I.	—	26	31	1	—	—	+	P.	G.	M.I.	2
130	16	—	1	+	++	P.	G.	?	—	33	44	3	—	—	++	G.	G.	P.	2
134	14	1	—	—	++	P.	G.	M.I.	2	46	11	—	1	—	++	G.	G.	M.I.	1
										48	19	—	—	+	++	G.	G.	M.I.	1
Pericarditis										54	17	—	—	—	++	G.	G.	P.	4
81	8	1	—	+	++	P.	P.	P.	—	55	24	2	—	—	++	P.	G.	I.	3
										59	24	1	—	—	++	G.	G.	P.	4
Enlarged Heart only										66	44	3	—	—	++	G.	G.	I.	1
80	26	1	—	—	++	P.	G.	I.	—	70	34	—	—	+	++	P.	G.	M.I.	2
85	14	—	—	+	+++	P.	G.	I.	—	74	24	Scarlet Fever			++	G.	G.	?	2
										94	9	2	1	—	+	P.	G.	I.	2
										100	14	1	1	—	++	P.	G.	I.	1
										104	14	2	2	+	++	P.	G.	M.I.	1
										114	15	—	1	—	++	P.	G.	I.	2
										124	6	1	—	+	+	P.	G.	I.	2
										133	8	—	1	—	++	P.	G.	M.I.	1

Explanation of Figures in Tables

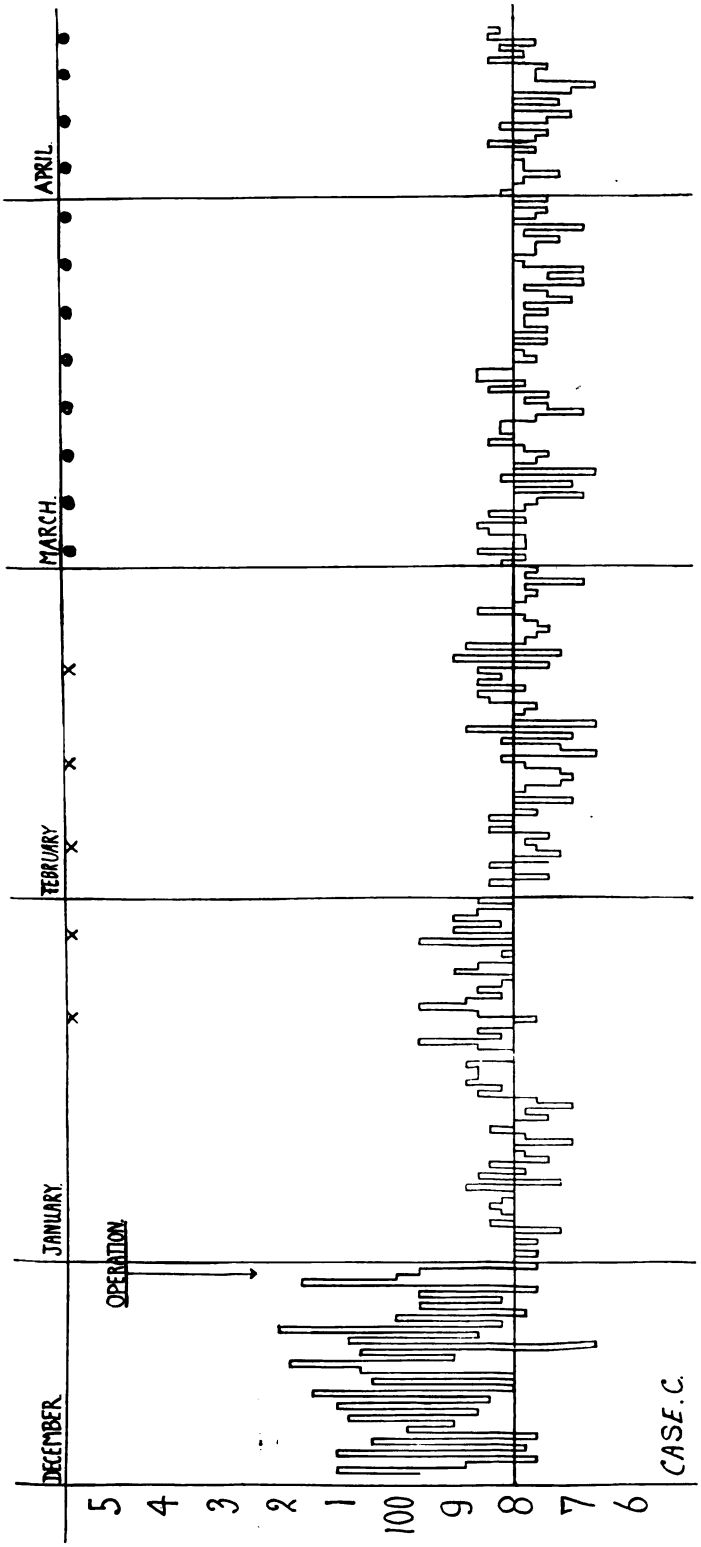
Number. The numeral represents the number in the Case Book.
Rheumatic Fever. The figure refers to number of attacks.
Chorea. The figure refers to number of attacks.
Tonsillitis. The sign + represents past or present Tonsillitis.
Enlarged Tonsils. One or more +, significance explained in Text.
Colour. P = Pale. G = a healthy red colour.
Progress P = lesion progressing unfavourably, + rapidly.
S = stationary.
I = improvement.
MI = marked improvement.
Degree of Stenosis. Value of numerals explained in the text.
A negative Wassermann was obtained in all the aortic cases without mitral stenosis or a clear rheumatic history, in these two tables.

Note on the Temperature Charts

These charts have been prepared on the plan devised by A. J. Hall and J. S. C. Douglas (*Quart. Journ. Med.*, xvi. 22, 1922).
The paper is ruled in inches and divided into tenths.
Each degree Fahrenheit occupies one inch vertically.
Each day occupies one-fifth of an inch horizontally, *i.e.*, one-tenth for the morning, and one-tenth for the evening record.
At the end of each calendar month, a vertical line is drawn, so that although each date is not recorded, yet the temperature of any particular morning or evening in any month can be ascertained by simple measurement.

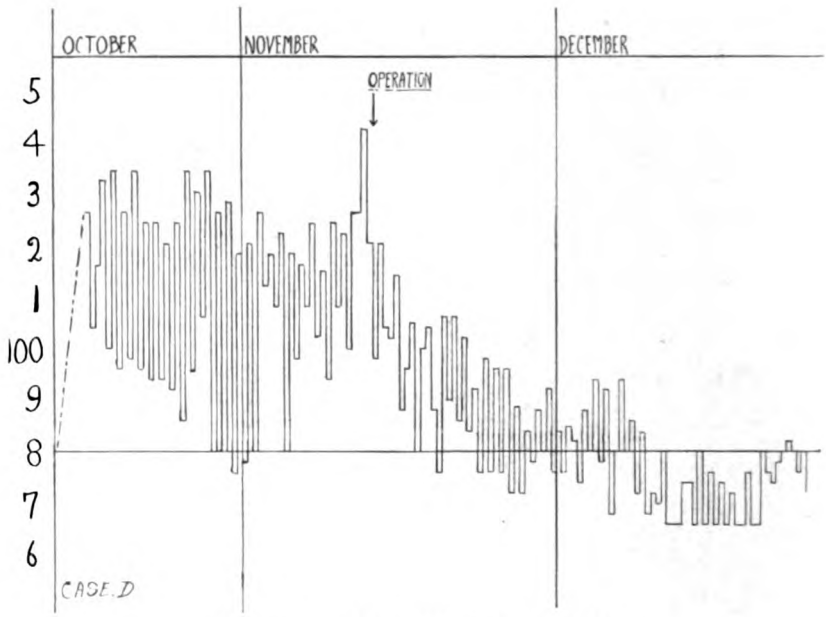


Temperature Chart I. See page 392.



Temperature Chart II. See page 392.

NOTE.—Each cross under the line of months represents an injection of vaccine, each circle on the same level an intravenous injection of peptone.



Temperature Chart III. See page 393.

CARDIAC MURMURS AND THEIR CAUSATION

By J. M. GILL, M.D., Senior Physician to the Sydney Hospital.

MURMURS about the heart, although extremely various, are probably all due to one cause. They will be dealt with in this order—

1. The Presystolic Murmur.
2. The Murmurs in Rheumatic Heart Disease in Children.
3. The " To and Fro " and other Aortic Murmurs, and the Murmurs of Aortic Stenosis.
4. Murmurs in Aneurysm.
5. The Murmurs of Congenital Heart Disease, including those of Ductus Arteriosus.
6. Hæmic Murmurs.

The literature is enormous and much is merely controversial, that on the presystolic murmur especially so. Fagge's paper in the *Guy's Hospital Reports* for 1871 should be consulted together with Wilks' paper in the same volume, as it is highly instructive for the historical side. Galabin's paper in the *Reports* for 1875 contains some excellent cardiograms, and deals with the presystolic murmur in some detail, opposing Fagge's view that it must be dependent on the contraction of the auricle. A good deal of the paper deals with the opinion, then advocated by Barclay, that the presystolic murmur was ventricular. In 1890 Goodhart published an interesting paper in the *Reports* on " Bruits," which discusses some of the difficulties; another paper was published by him in 1893 on the same subject. I have not discovered any more recent papers in the *Reports* on this subject.

Two articles were published by me in the local Medical Journal in 1909 and 1911. This paper is now written because recent work has rendered possible a much more comprehensive view of the whole subject.

1. *The Presystolic Murmur*

It seems incredible that the presystolic murmur was virtually not known before Gairdner's description in 1862. Stokes in 1854 dismissed it with a single casual reference as not worthy of serious attention. Fagge's paper in 1871 is a model of what

such a paper should be. He gives details of a large number of cases, fatal and otherwise. He says that the murmur can only be explained as being due to the contraction of the auricle, and that the contraction is unduly prolonged. He, and Wilks in the same volume, both recognise, of course, that that was not the sole explanation; that the murmur must in part be due to the passive flow of blood through the narrowed orifice. The idea that the passive flow of blood caused the murmur was adopted by Galabin. The difficulty with all these writers was to explain how so prolonged a murmur could be caused by the contraction of the auricle, normally so brief. Fagge's idea that the contraction of the auricle occurred at the end of the cardiac cycle instead of at the beginning was not generally accepted. It was thought that only the final accentuation of the presystolic murmur was due to contraction of the auricle, the rest of the murmur being due to the passive flow of the blood through the narrow orifice.

Fagge and Galabin both taught that the presystolic murmur was not present apart from mitral constriction. They did not seem to be aware of Austin Flint's paper, published in 1867. Balfour, in the first edition of his book in 1876, mentions Flint's view, but looks upon it as a heresy. Since then it has become universally accepted. In the first edition of Allbutt's *System of Medicine* (1898) Flint's murmur is clearly described and the different theories explaining it are set out. It is enough to say here that it may resemble the presystolic so closely that mitral stenosis has been diagnosed by competent observers in cases of aortic insufficiency, when the mitral valve has been found to be perfectly normal after death.

Another condition, which is well known to produce a presystolic murmur now and again, is adherent pericardium. It is certainly not common, but it is mentioned in most of the text-books. Such a case presented itself to me several years ago. A man aged twenty, who had had rheumatism, and had been under treatment for mitral stenosis two years before, and for pericarditis about eighteen months before, came under my care in December 1906, as an out-patient. He was very short of breath, and the heart was much enlarged. The murmurs are described as systolic and diastolic at the apex. As he did not improve under out-patient treatment, he was sent into the hospital on January 7; under the usual treatment rapid improvement took place. On January 19 a diastolic apical thrill and a presystolic apex murmur appeared. He became worse again and died with dropsy on March 1, 1907. Post-mortem examination showed the heart much dilated and hypertrophied on both

sides. The layers of pericardium were universally adherent to each other, but not to the thoracic wall. The mitral valve was thickened and incurved a little, but there was no actual stenosis. The other valves were normal. The right auricle was enormously dilated. This case was regarded during life as one of mitral stenosis without any doubt, and after death as a case of adherent pericardium. It is to be noted that the mitral valve was the only one diseased, but the amount of disease was trivial. I shall return to the real significance of such cases as this later on.

With regard to the connection between the presystolic murmur and the contraction of the auricle, I presume that almost everyone will admit that it is in some way dependent upon the activity of the auricle. The view that it is ventriculo-

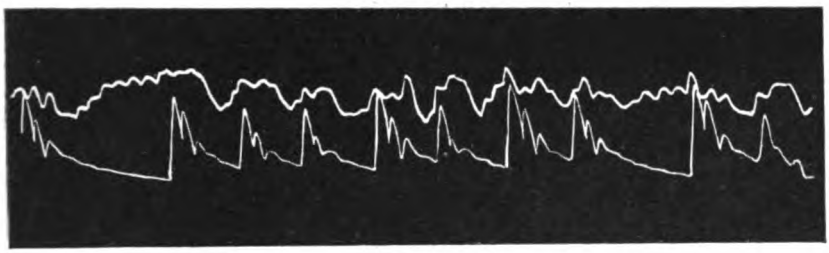


FIG. 1.

Venous pulse and *Radial tracing.* Auricular fibrillation with presystolic murmur.

systolic and not auriculo-systolic need not be seriously considered and can now be dismissed without any further consideration. Mackenzie states positively that in mitral stenosis it is due to the contraction of the auricle, and that in cases in which the auricle does not contract, but has gone into fibrillation, a presystolic murmur, if previously present, disappears; that the presystolic murmur is, in fact, an indication that the left auricle is acting normally. When fibrillation sets in the only murmur audible is a "diminuendo" diastolic murmur, due to the passive flow of blood through the narrow mitral orifice. Such a view explains why in advanced cases of mitral stenosis there may be no murmur at all or only a diastolic murmur of the "diminuendo" type. But some cases of auricular fibrillation have a presystolic murmur. I had such a case in an elderly man of about sixty, who had very few signs of heart failure, beyond a slight degree of breathlessness and some cyanosis. A typical presystolic murmur was constantly present. Venous pulse tracings showed curves typical of auricular

fibrillation, the fibrillary waves being unusually distinct (Figs. 1 and 2). These fibrillary movements were also well shown in cardiograms taken from the apex and the epigastrium. The radial pulse was generally about normal rate, slowing down

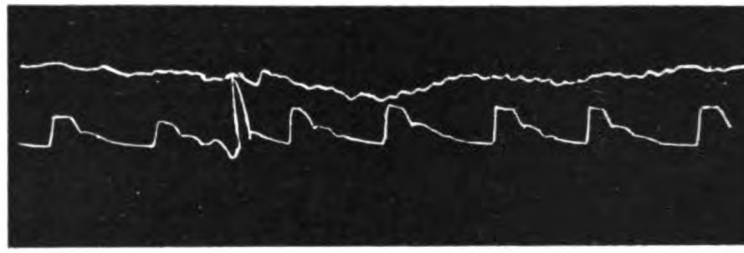


FIG. 2.

Apex and *Radial tracing.* From the same case as last tracing. Fibrillary movements at the same rate in each tracing, 450 per minute.

readily to about 60 under treatment with digitalis, and, as usual in auricular fibrillation, it was never regular. Yet the presystolic murmur would fill up the whole interval. Such cases as this are exceptional.

2. *The Murmurs in Rheumatic Heart Disease in Children*

I have said " in children " in order to exclude complications that come on in later life owing to secondary changes in the valves. The problem is therefore somewhat simplified. The usual systolic apex murmur varies a good deal in intensity. Generally speaking the more severe the rheumatic infection, the greater the hypertrophy of the heart and the louder the murmur. In the more severe cases a double murmur, systolic and diastolic, commonly called a " to and fro " murmur, is often present. In many cases it is difficult to describe exactly what one hears. Thus, in addition to the ordinary systolic murmur, there may be a rumble occupying the whole period of the cardiac action, systolic and diastolic, evidently of deeper origin than the ordinary murmur, and seeming to arise from a deeper source. In one such case, with a greatly hypertrophied heart and a thrill at the apex, the murmur is described as a harsh, rough, continuous, tingling murmur, which resembles a " to and fro." If traced upwards this murmur is abruptly lost at the level of the third left interspace. The second sound is clear in both the pulmonary and aortic areas. There are no special murmurs at the base. The boy, aged ten years, when admitted was suffering from a considerable degree of heart failure, with a greatly enlarged

pulsating liver; under treatment the symptoms rapidly subsided and he was discharged after six weeks in a very satisfactory condition. The murmur was exactly the same during the whole period of his stay in the hospital. In another case, similar to the last, there was audible about half-way between the left sternal border and the nipple, a continuous, tingling sound only, not a murmur. In most cases this continuous, tingling sound is accompanied by a systolic murmur at the apex. It must be admitted that it is very difficult to describe murmurs and similar sounds at all accurately. In actual practice most people classify murmurs into systolic, diastolic, etc., without going into the actual significance of sounds, the origin of which is not clear. My object in this paper is to describe as well as I can some of these abnormal sounds, and finally to give what I think is a reasonable explanation of the more familiar murmurs.

The most common murmur after the systolic at the apex is the diastolic. The latter generally is a soft, blowing " diminuendo " murmur, following the second sound and ceasing before the first sound of the next cardiac cycle. This is generally limited to the apex and the neighbourhood, and it generally disappears altogether after the usual rest in bed. In some patients who have been readmitted after an interval this murmur has disappeared. In one case, of which I have preserved the notes, the diastolic murmur persisted, and the systolic disappeared. This case is worth a more detailed description. The child, a boy aged five years, was admitted to the Children's Hospital for an attack of acute rheumatism of ordinary severity, which soon subsided under treatment with sodium salicylate. The heart did not appear to be enlarged. " A low, soft ' to and fro ' murmur can be heard best in the third left interspace: these murmurs are only doubtfully audible at the apex." Four days afterwards it is noted that " the murmur to-day is a soft, low diastolic, audible best just internal to and above the left nipple: no thrill. The murmur is so soft that it is difficult to be sure of the rhythm." The child was kept in bed for two months in the hope that the murmurs might disappear, but they remained the same during the whole time. A diastolic murmur was always audible in the same situation, viz. the inner end of the third left interspace and over the right ventricle generally. There was no systolic murmur. The murmur was precisely such as is heard in aortic regurgitation, and the question arose whether that might not be the cause, but the pulse was not typical. It had all the characteristics of the mid-diastolic murmur of mitral stenosis—blowing in character, soft and diminuendo. There were no symptoms. This diastolic murmur

could not have been caused by mitral stenosis, which is unknown as a result of acute rheumatism at that age. I believe the same is true of aortic regurgitation. As I have already said, the early diastolic murmur is quite common in rheumatism in children at any age, when mitral stenosis as a pathological condition is almost unknown. Graham Steell describes the murmur in his book on heart disease, but candidly confesses that he can give no explanation of it.

In addition to these various murmurs audible over the chest wall at different places, very similar sounds can be frequently heard in the jugular veins in the neck. Murmurs in the veins are sometimes audible when none can be heard over the heart itself. It seems natural that murmurs arising in the heart should be transmitted to the veins as well as to the chest wall covering it, and such is the case. The abnormal sounds heard in the veins are generally very similar to the murmurs audible over the heart. Not infrequently a thrill can be felt, obviously very similar to the thrill which can frequently be felt at the apex and elsewhere. The murmurs in the veins may be present when there are none in the heart itself; the converse is also true. There can be no suspicion of anæmia in these cases, as the children are often healthy in every respect except for the rheumatic condition. Moreover, the anæmias, chlorosis and Addison's anæmia, which give rise to murmurs in the neck in the adult are practically unknown in children. We have thus in early cases of rheumatism in childhood a variety of murmurs, systolic and diastolic, most common of course at the apex, but audible elsewhere in the chest as well as in the neck. In addition, there is often a rumbling or tingling sound, quite different from the ordinary murmurs, audible at or near the apex, which may continue during the whole cardiac cycle at the same intensity and character. Thrills are common at the apex and at the base of the neck; they may be systolic or diastolic or sometimes continuous.

Finally, the heart may be diseased in the absence of any murmur. A murmur may develop subsequently. Now what is the explanation of these facts? The view almost universally held is that the systolic apex murmur is due to dilatation of the heart; the actual amount of regurgitant blood is supposed to be insignificant and therefore not capable of leading to any inconvenience to the subject. This doctrine, though plausible, does not stand investigation. There are two fatal arguments against it: first, that a systolic murmur is often, indeed usually, not accompanied by dilatation; secondly, that dilatation frequently occurs without any murmur. It is abundantly clear that all writers on this subject consider that murmurs can only

be explained by the fluid vein hypothesis, and exercise their imagination to fit the facts to that theory. The earlier writers on heart disease appear to have thought that cardiac murmurs were all due to valvular disease, and the idea that dilatation of the left ventricle may lead to imperfect closure of the mitral valve seems to have been of more recent origin. I believe that Balfour was responsible for the general adoption of that idea somewhere about fifty years ago. A little experience will soon show the inadequacy of such a view, as dilatation and a systolic murmur are not necessarily associated. Moreover, the diastolic murmur on the same hypothesis could only be explained by a narrowing of the mitral ring. We would have to suppose, in these cases of rheumatism in childhood, that the mitral ring narrows when the auricle contracts, but dilates when the ventricle contracts! Moreover, how could we explain the continuous tingling murmur already described or the murmurs audible in the veins of the neck?

3. *The "To and Fro" and other Aortic Murmurs; and the Murmurs of Aortic Stenosis*

I shall take the aortic systolic murmur for discussion first. It is well known that this murmur is often present when there is no disease of the aortic valves. In cases of valvular aortic disease, producing a "to and fro" murmur, there is rarely any actual stenosis, although the systolic murmur is generally well marked.

There are many difficulties about the ordinary "to and fro" aortic murmur. Firstly, it may be present when the valves are healthy. Finlayson in 1884 described two cases of this nature; and Goodhart, in his paper on "Bruits" already referred to, discusses the occurrence of diastolic murmurs in the pulmonary and aortic arteries, the sigmoid valves being healthy. I strongly advise my readers to consult this highly interesting and instructive paper. There is no doubt about the fact. In elderly men it is not uncommon to hear such murmurs in subjects showing no signs of heart disease whatever, the murmurs being detected on routine examination. It seems to me impossible to suppose that the aortic valve is diseased in the total absence of all symptoms and with a normal pulse and no hypertrophy of the heart.

Secondly, the sounds may be normal when the valves are diseased. It is not uncommon for cases to be admitted with a considerable degree of heart failure, really due to disease of the aortic valves, with sounds at the base quite normal, the true

nature of the case being revealed later on after some degree of recovery has taken place. For instance, a man aged forty-two was admitted to hospital for heart trouble. There was a history of rheumatism. On admission, it was noted that the apex beat was in the mid-axillary line. There was a diastolic murmur at the apex of a blowing character. After he had been in a few days, a "to and fro" murmur was audible at the base in the aortic area and down the sternum to the right, but it was louder to the left of the sternum. The man soon lost all his symptoms under the usual treatment. It is a well-known fact that in dying patients, suffering from aortic valvular disease, the "to and fro" murmur may be absent.

The characteristic murmur of aortic stenosis is a rough, prolonged systolic murmur, with or without a thrill, loudest in the aortic area. The pulse is slow and markedly anacrotic.

FIG. 3.

Fibrillary movements are well marked and occur at the rate of 8 per second.

At a post-mortem examination the valves may be calcareous with a small central aperture allowing free regurgitation. Of course there is no difficulty in understanding the systolic murmur, but why should the diastolic murmur be wanting altogether in so many cases? In some cases, moreover, of aortic stenosis the most noticeable murmur may be a systolic murmur at the apex, leading to the diagnosis of mitral regurgitation. But it should always be remembered that the murmurs may vary considerably from day to day. The details of one such case are worth recording. A man aged fifty-seven years came under my care in March 1909, and remained continuously under observation till his death in November 1910. I was at that time carefully studying the subject of murmurs, and every time he called to see me I carefully noted the condition of his heart. The pulse was regular and slow, generally about 40 per minute, slowing down to 36 at one time, but rising to 84 or 88 at others. The increased rate was sometimes due to extra-systoles, but not always. The radial pulse was anacrotic. Venous pulse tracings

and cardiograms were readily obtained. The venous pulse showed the normal $a - c - v$ sequence, but the cardiograms were most instructive (Fig. 3). When first seen on March 16 there was a loud systolic and a faint diastolic murmur in the aortic area. The heart was not much hypertrophied. Similar murmurs were heard at the apex. On April 8 he was treated for an attack of gout. On April 12 there was a harsh, loud systolic murmur at the apex, limited to the immediate neighbourhood; in the aortic area a soft, blowing systolic and a very faint diastolic murmur, which was also heard at the apex. The loud murmur disappeared altogether as it was traced from apex to base. On July 28 it was noted that the systolic murmur was as on April 12. No diastolic murmur could be heard at the base; at the apex and limited to it could be distinctly heard a distant very rapid series of sounds, very like fœtal heart sounds, but much more rapid. On September 16, 1910, there was a soft, blowing systolic murmur in the aortic area; no diastolic murmur was audible, as the pulse was rather rapid owing to an attack of bronchitis. At the apex and limited to its immediate neighbourhood there was a very loud, harsh, rough murmur accompanied by a doubtful thrill. This murmur was partly systolic and apparently partly presystolic, but lacked the crescendo character of a presystolic murmur, and it was difficult to determine its precise relation to the carotid pulse. The murmur was prolonged, occupying almost the whole cardiac cycle, and was of uniform character throughout. On September 28 the usual systolic murmur was heard at the base in the aortic area, now followed by a blowing diastolic, the pulse rate being much less than on September 16. At the lower end of the sternum to the left a very definite to and fro murmur could be heard. At the apex the harsh murmur already described was present as before, but seemed rather presystolic. On October 5 there was a typical rough, presystolic apex murmur. The to and fro murmur could be heard over a wide area, both at the base and towards the apex. On November 3 it was noted that there was a rough presystolic murmur and a blowing systolic murmur at the apex. Inwards from this the systolic murmur disappeared and only a rough, grating murmur was heard. The murmurs at the base and the lower end of the sternum were unaltered. Death took place from heart failure shortly after this last note was written. No post-mortem examination was allowed. The diagnosis was aortic stenosis and probably mitral stenosis as well. But the point on which I wish to lay stress is the variability of the murmurs. Few of us, I think, realise how murmurs in chronic heart disease vary. I have come to the conclusion that the

classification of murmurs into systolic, diastolic, etc., though convenient, is inadequate and artificial. Murmurs are sometimes continuous during the whole cardiac cycle; at other times, as in this case, they appear to be partly systolic and partly diastolic. At the apex the altering relation of the heart to the chest wall is a very disturbing factor; a murmur may be continuous during the whole cardiac cycle, and yet the withdrawal of the apex from the chest wall during diastole will give it a " to and fro " character. Finally, before leaving the subject of aortic stenosis, I might mention the fact that cases of aortic stenosis may be diagnosed as cases of mitral regurgitation, because the only murmur heard is a systolic murmur at the apex. W. H. Dickinson published four such cases some years ago.

4. *The Murmurs in Aneurysm*

I believe that no murmur of any kind, systolic or diastolic, is audible in cases of thoracic aneurysm unless the aortic orifice is involved. During the last fifteen years I have seen several cases of thoracic aneurysm, and not a single case has presented a murmur when the aortic valve was normal. There is, I think, a general belief that a systolic aortic murmur may indicate the presence of an aneurysm. I am convinced that this is a mistake. It is interesting to note that so long ago as 1854 Stokes of Dublin made the same assertion as I do. But he also says that a murmur may occur in aneurysm of the abdominal aorta. I have had no opportunity of verifying this statement, as no such case has come under my observation during the period covered by this inquiry.

5. *The Murmurs of Congenital Heart Disease*

I have the notes of a great number of such cases. Most of the severe cases only survive a few months or three or four years at most. I shall be content at present merely to summarise my experience. In spite of the very great variety of pathological lesions, in the great majority of cases the clinical condition is almost the same. The murmur is usually a loud prolonged systolic, occupying almost the whole cardiac cycle, loudest at the base near the sternum at about the inner end of the third costal cartilage, but not infrequently loudest at the apex. In some of my cases it has been at one time loudest at the base, at another at the apex. There is almost always considerable hypertrophy of the heart, the right ventricle becoming of equal size to the left. Thrills are common both over the heart and in the neck. The lesion in these cases is no doubt most often a patency of the inter-ventricular septum. The murmur is

usually explained as being caused by blood escaping through the opening from the left ventricle to the right, an obviously unlikely happening, as it would be merely a question of time when all the blood would be in the pulmonary circulation. Again, it is exceedingly unlikely that the left ventricle is more powerful than the right, as the two ventricles have usually walls of equal thickness and apparent strength.

The murmur of persistent ductus arteriosus needs special mention. Goodhart, in the paper on "Bruits" already referred to, discussed it fully. More recently Gibson of Edinburgh called attention to it. The characteristic murmur is a continuous humming sound occupying systole as well as diastole; other writers describe it as a prolonged systolic murmur, audible below the left clavicle in the position of the patent ductus. I have had only one such case which has come to the post-mortem room. This was a child, three years of age, under observation at the Children's Hospital for many months. The characteristic murmur as described above was audible and led to the diagnosis of patent ductus. The child ultimately developed infective endocarditis and died. The post-mortem examination showed an aneurysmal dilatation, about the size of a walnut, of the ductus arteriosus. This communicated freely with both the aorta and pulmonary artery. Goodhart quotes a case in which a very similar murmur was heard, and the only lesion found post-mortem was an enormously dilated pulmonary artery; the semilunar valves were normal. It is difficult, as he says, to see how such a murmur, as much diastolic as systolic, could be generated in a narrow pipe between the aorta and the pulmonary artery. I have never heard this murmur in congenital heart disease in infants except in the one case already quoted, and only three or four times in adults. As a patent ductus is one of the common lesions in congenital heart disease, I have come to the conclusion that perhaps the murmur only occurs if there is an aneurysmal dilatation, as in the case quoted above. As this murmur very closely resembles that heard in arterio-venous aneurysm, and in cases where an aortic aneurysm has ruptured into the pulmonary artery or superior vena cava, the one explanation must obviously apply to each.

6. *Hæmic Murmurs*

The "venous hum" in the neck in its fully developed form is a continuous murmur. It is often more like a roar than a "hum." To bring it out well it is usually necessary to make the patient sit or stand up. It is often accompanied by a thrill.

Though the right jugular bulb is the best place to hear it as a rule, the left jugular also often yields it. Sometimes the murmur and thrill are present in the episternal notch.

It is constantly present in Addison's anæmia, and frequently in secondary anæmias and chlorosis.

Hæmic murmurs are frequently audible over the precordium, in the pulmonary area most often, then the apex, and lastly the aortic area. These murmurs are probably always systolic; but they are often absent over the chest wall, when they are well heard in the neck over the jugular.

Extraordinary ingenuity has been expended in adapting the fluid vein hypothesis to explain these murmurs. The very multiplicity of theories shows the difficulty. The venous hum in the neck is explained by saying that the vein in its passage through the deep cervical fascia in kept patent, but collapses above and below it. The blood travels along in an uneven stream and so produces eddies. But that explanation obviously does not apply to the murmur sometimes heard in the left innominate vein; nor does it explain why the murmur is perfectly constant in character in typical cases. Further, the murmur is best brought out by pressure with the stethoscope, sufficiently firm to stop the flow of blood through the vein. Lastly, the murmur should be heard below the opening in the deep cervical fascia and not above it. I think that one may say that this explanation is inadequate. The systolic murmur in the pulmonary region has also received a great amount of attention, and several explanations thereof have been advanced. I do not think that any of these are worth serious notice. The systolic murmur at the apex has been ascribed to dilatation of the left ventricle. But there is never any evidence of dilatation, and it is obvious that this explanation was introduced to fit in with the usual theory of murmurs. The systolic murmur in the aortic area has also never been adequately explained. There is essentially no difference between hæmic and other murmurs as far as the quality of the sound is concerned. The usual teaching is that if the systolic murmur at the apex can be traced out to the axilla, mitral regurgitation is present. That has always appeared to me an irrational statement, as the audibility of the murmur in the axilla must depend chiefly upon the relation of the apex beat to the chest wall.

Now, if the fluid vein theory be inadequate to explain cardiac murmurs, what is there to take its place? I believe that there is an adequate explanation, which is quite simple and which, if clearly understood, will help one to understand much that is obscure in heart disease.

I shall take the presystolic murmur first. In the case already described, the tracings from which have been given, the fibrillations of the auricle are perfectly regular, and continue during the whole cardiac cycle at the same rate of 450 per minute. This man was under my observation for years, and I saw him very frequently and took numerous tracings, all of which showed these waves. Cardiograms from the apex and the epigastrium also showed them, perfectly regular and at exactly the same rate of 450. It was clear, of course, that the movement in the neck was muscular in origin and that it came from the right auricle; it was also clear that the waves shown in the cardiograms must also come from the same source, as the two movements appeared to resemble each other in every way. I then conceived the idea that a similar movement arising in the left auricle could produce a presystolic murmur. It is clear that the more important factor in the presystolic murmur is the hypertrophy of the left auricle, not the narrowing of the orifice; I imagined also that a certain degree of tension of the walls of the auricle is necessary for the production of the sound, and that such a sound would increase in loudness with the increase in tension, and again that the sound would be conveyed to the apex by the blood stream and would be abruptly terminated by the contraction of the ventricle. Such a murmur would, of course, be limited to a small area round the apex and would be made louder by exertion.

I adopted a similar method of examination with other cases showing a presystolic murmur. I often found indications of these waves in venous pulse tracings and in cardiograms. They were generally much best recorded from the precordial area away from the apex towards the base and nearer the left border of the sternum. They are delicate and easily obliterated. To make them obvious it may be necessary to get the patient to sit up and lean forward a little.

Venous pulse tracings are not so suitable as cardiograms for recording them, as a good deal of pressure is often required to get a satisfactory record of the venous pulse. Cases of heart-block are very suitable, the long interval between the beats preventing confusion. Fortunately such a case presented itself to me. The patient was a boy, aged ten years, admitted to hospital in December 1908 for acute rheumatism. When I first saw him an operation for appendicitis had been performed the previous day; he was then suffering from an exceedingly severe attack of acute rheumatism, several joints being affected. The pulse was normal in frequency and rhythm. There was no murmur. Under the usual treatment with sodium salicylate the arthritis promptly disappeared. He was then transferred back to the

surgical ward, as the wound had not healed. I was asked to see him again in a few days, as the pulse had become very slow. He then had a pulse of 36, perfectly regular, the venous pulsation in the neck being very evident. The heart was beating forcibly with the apex beat about one inch outside the nipple line. There

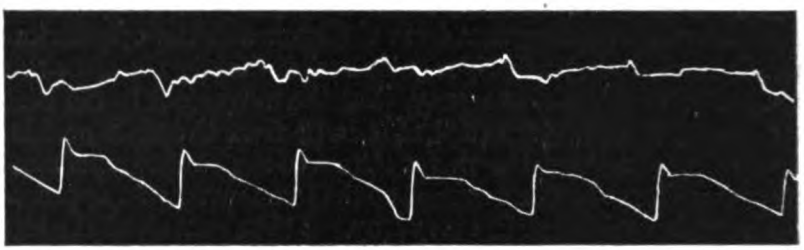


FIG. 4.

Cardiogram and *Radial tracing*. Heart-block. Cardiogram taken internal to the apex beat, as described in the text.

was no murmur. As the appendicitis wound had healed, he was transferred again to the medical ward under my care, where he remained until he was discharged three months afterwards. There was never any murmur; venous pulse tracings showed complete heart-block. The ventricular rate varied between 40 and 60, the auricular rate being about twice that of the ventricular. The heart-block once established remained constant,

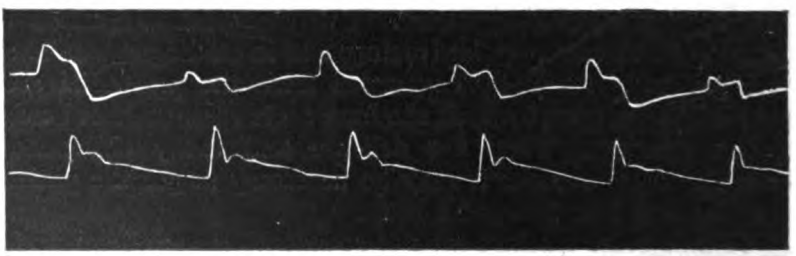


FIG. 5.

From the same case as the last figure. The cardiogram was taken from the apex, which was rather forcible.

the radial pulse being usually about 50. He had no subjective symptoms, went to school and played games like other boys. After discharge I used to see him from time to time for about two years, but his condition did not vary. I did not at first look upon this case as other than one of heart-block; but, taking tracings one day from the apex beat, I accidentally placed the receiver over the right ventricle, towards the base, and got the record shown here (Figs. 4 and 5), which shows the fibrillary

movements quite clearly. The record from the apex is shown as a contrast; in this there is no trace of the fibrillary movements. I naturally thought at first that it was some accidental tremor, either of my own hand or of the pectoral muscle, which had been recorded. But I found I got the same result with each tracing I took. To prevent any error I then placed the receiver on the boy's shoulder, on the right side of the chest, and got a straight line every time. It was now clear, of course, that these movements came from the right auricle and were of muscular origin, and continued through systole and diastole at the same rate, and were very regular. I found that they numbered eight per second, the rate appearing to be constant. Records of these waves were easy to procure; I have tracings in this case up to July 16, 1909, several of which show them very well. It was not clear to me at first why these vibrations should be continuous when murmurs are usually discontinuous. Further reflection brought to my mind the thought that the venous hum of chlorosis was continuous and had never been explained. The whole mechanism of the production of murmurs at last became clear. The only one, of which I had had previously a clear idea, was the presystolic. The key to the whole series of murmurs was given by the murmurs of anæmia. The bell of the stethoscope placed over the right jugular bulb lies very near the junction of the superior vena cava and right auricle; all movements in the auricle are readily transmitted to this area, since there are no valves separating the vein from the auricle. The thrills so often felt in the neck must also arise from the right auricle, as clearly shown by their being sometimes felt over the left innominate vein in the episternal notch. It is evident that the murmur is continuous; and it is also evident that the thrill is continuous. It is clear that the vibrations and murmur have the same origin, and that they can only come from the right auricle. I think the venous hum is the murmur in its completest form. It often has to be made evident by making the patient sit up in bed or stand, showing that the vibrations are transmitted to the neck by the wall of the vein, principally at any rate; the effect of the erect posture is to empty the vein and to make it more taut. In my experience the most common murmur is the apical systolic, because when the ventricle contracts any vibrations communicated to it by the auricle are most readily transmitted to the chest wall at the apex, this being the area at which the heart knocks against the ribs. The systolic murmur in the pulmonary area is also common, because that is the area occupied by the infundibulum of the right ventricle. The aortic "to and fro" murmur is simply

an indication that the aorta is dilated, or, perhaps also more probably, that there is hypertrophy of the heart. But once

FIG. 6.

Apex beat and *Radial tracing.* Rheumatic heart disease. Heart much hypertrophied. Loud rough murmur.

these vibrations are admitted, it is easy enough to see how murmurs can be produced.

In rheumatic heart cases with much hypertrophy, these vibrations are generally very evident and very easy to record.

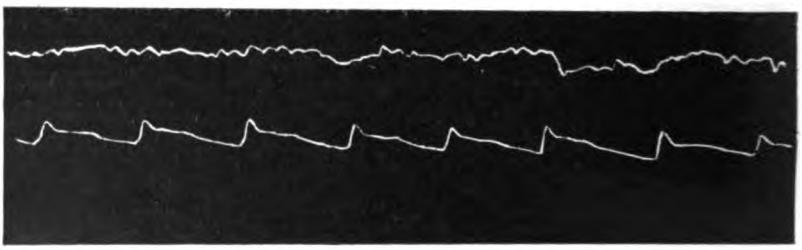


FIG. 7.

Apex and *Radial tracing.* Similar to last; but less hypertrophy.

In milder cases, where the hypertrophy is slight, they are not so obvious, but I have often succeeded in showing them. In such cases it has appeared to me that they become feebler as the interval since the rheumatic attack increases; the same is often true of murmurs.

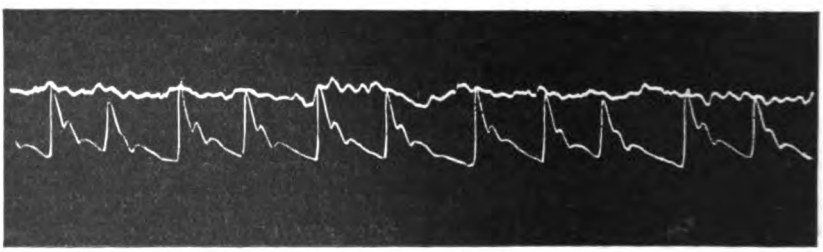


FIG. 8.

Cardiogram and *Radial tracing.* Auricular fibrillation. Systolic murmur.

In cases of auricular fibrillation they are often very evident but are generally quite regular and always at about the same

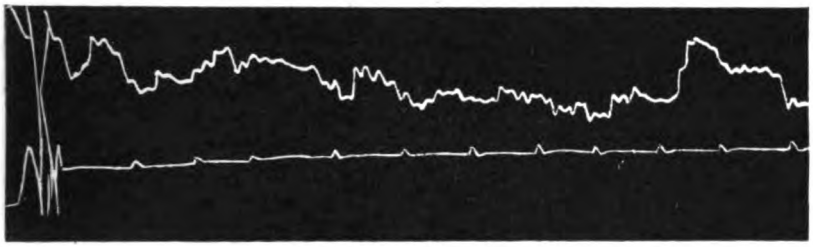


FIG. 9.

Cardiogram and *Radial tracing.* Auricular fibrillation. Systolic murmur.

rate—480 per minute. In fact the constancy of the rate and the regularity are remarkable.

They are often easy to get in old people. I have several

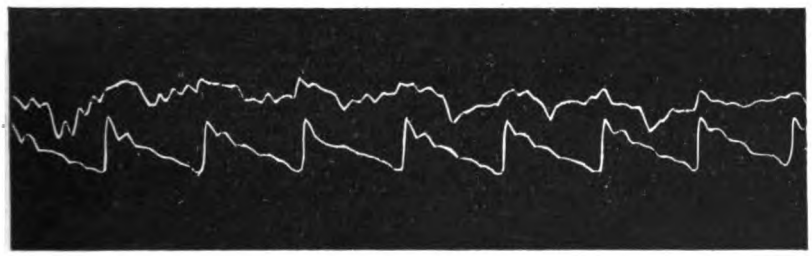


FIG. 10.

Cardiogram and *Radial tracing.* Chronic Bright's disease. No murmur. Heart hypertrophied.

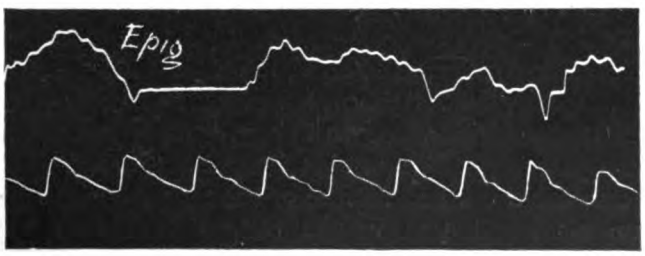


FIG. 11.

Epigastric and *Radial tracings.* "Senile" heart. Loud systolic murmur, internal to apex.

records showing them in congenital heart disease. I have not examined many cases of anæmia for them, but I have one case of chlorosis which shows them well, and cases of Bright's disease show them particularly well. One can, in fact, record them in

all sorts of cases in which murmurs are common. They are also to be met with in cases, as of rheumatism, where there is no murmur, but in which one knows that the heart is affected; for instance, in addition to the case of heart-block already mentioned, I succeeded in recording them in a case of rheumatism in a boy, who developed paroxysmal tachycardia during convalescence.

I shall now state the reasons why I consider these vibrations to be of muscular origin. As I have already said, they are very easy to record in cases of auricular fibrillation. Recently it has been shown that direct leads from the chest wall in auricular fibrillation show them better than any others, if the electro-cardiograph is used. The waves are the same in rate whether the polygraph or the electro-cardiograph is employed, and the best place to secure a good record is the same. But we find that the polygraph also records precisely similar movements in other forms of heart disease, renal disease and anæmia. These records are essentially all of the same rate and obtained in precisely the same way. When we compare the clinical records of murmurs with post-mortem results it is, I think, obvious that no mere mechanical explanation can possibly be adequate. Something more is necessary, and that is furnished by these records.

It is necessary to discuss the physiological aspect. These vibrations cannot be demonstrated in the normal subject. Under pathological conditions, *e.g.* anæmia and acute rheumatism, they make their appearance. I imagine that they are dependent upon the activity of a more primitive tissue normally kept in abeyance by the more highly developed striated tissue of the auricle. The two kinds of muscular tissue are evidently united. In fibrillation of the auricles, the striated muscle is paralysed, but the fibrillary movement, being more primitive, continues.

The similarity in the behaviour of voluntary muscle and of the auricle is obvious, for in progressive muscular atrophy we have a pathological demonstration of the process. Fibrillary movements are a marked feature of the muscles in this disease; they are also well seen in the tongue in bulbar paralysis, continuing uninterruptedly till the muscular fibres are completely atrophied. Following the teaching of Hughlings Jackson, one looks upon this fibrillary movement as one that is normally kept in check by the more highly developed function under the control of the will. The fibrillary contraction is thus the most primitive form of activity shown by striated muscle. The heart muscle, of course, does not undergo complete atrophy, and hence fibrillation continues indefinitely. The unit in the voluntary

system is the neurone, not the muscle merely. On the other hand, the heart is the unit, not dependent on any structure external to itself for life, but containing its own ganglia and nerves. Now what is true of the auricle is also true of the ventricle. Fibrillation occurs in the ventricle as well as in the auricle, but, of course, shortly ends in death unless the normal rhythm is restored.

That there are two kinds of muscle in the hearts of some animals, amphibia, has been definitely proved. W. H. Gaskell, in his posthumous work on *The Involuntary Nervous System*, brought the facts together in a most convincing way. I must refer readers to this work for the physiological details. Here it is sufficient to say (quoting Gaskell) that " these observations definitely prove the existence in the heart of a system of unstriped musculature, in addition to the striated cardiac muscles, which is especially well developed in the water-tortoises, and extends from the auricles into the beginning of the great veins. This unstriped muscle resembles the enteral unstriped muscles, the bronchial muscles and those of the gall-bladder, in its behaviour to poisons like atropine and muscarine and in its innervation; for all these muscles are supplied with motor fibres from cells connected with the vagus outflow, and with inhibitory fibres from cells connected with the thoracico-lumbar (*i.e.* sympathetic) outflow. On the other hand, the striated cardiac muscle resembles the enteral sphincter muscles in that their motor nerve-cells are connected with the thoracico-lumbar outflow, and their inhibitory cells with the vagus outflow. In fact, exactly the same kind of reciprocal innervation exists in the heart as in the intestine, and this fact suggests in the mind of the observer the same question : were the vagus and sympathetic cardiac nerve-cells, which have travelled out from the central nervous system, originally nerve cells, whose axons divided into two nerve fibres, of which the one was motor or inhibitory to the unstriped cardiac musculature, and the other inhibitory or motor to the striated cardiac muscle? The disappearance of the unstriped muscle in the higher vertebrates would bring about the disappearance of its motor and inhibitory nerves, and leave the vagus cells inhibitory to the heart muscle, and the sympathetic cells motor or augmentor to it." With reference to the last paragraph, I think that one is justified in asserting that the unstriped muscle has not disappeared in man. There is undoubtedly a reciprocal action between the movements of a fibrillating auricle and the ventricle. For instance, stimulation of the vagus leads to an augmentation and quickening of the movements of the auricle, at the same time as it slows the

ventricular contraction. Atropine has exactly the opposite effect, slowing the fibrillary movements and quickening the ventricular contractions. A very similar reaction to drugs and vagal stimulation has been described in man to that described in the paragraph quoted from Gaskell.

The assumption that the auricle contains two kinds of muscle, the one more primitive and the other more highly organised, gives a simple explanation of many clinical facts otherwise difficult to understand. For instance, paroxysmal tachycardia becomes quite easily understood. It should be looked upon as an intermediate stage between the normal rhythm and fibrillation, the auricle responding to a stimulation which normally does not reach it. (It is to be supposed that in health there is a " block " between the two kinds of muscle.) It also explains why digitalis does not act upon cases showing this rhythm, as stimulation of the vagus tends, if anything, to increase the frequency of the fibrillary movement and not to slow it. It has always been difficult to understand why digitalis does not act upon the normal heart even in large doses. If one supposes that the striated muscle, with its nerve the sympathetic, is in some way weakened or poisoned in rheumatism, it is easy to understand how murmurs make their appearance and how digitalis acts. The activity of the smooth muscle is normally completely inhibited, but in rheumatism it is unmasked as it were, and exposed to the influence of drugs like digitalis. In the form of irregularity now generally known as auricular fibrillation, the striated muscle in the auricle is completely paralysed, and hence the smooth muscle acts unchecked; the effect of digitalis is thus more obvious and more easily demonstrated than in other forms of heart disease.

THE GASTRIC GERMICIDAL BARRIER

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IN view of the importance attached to the presence, temporary or permanent, of pathogenic bacteria in the alimentary canal, points of interest inevitably arise in connection with the exact effect of the gastric secretion upon swallowed micro-organisms.

The antiseptic action of the gastric juice was noted more than one hundred years ago by Spallanzani.[1] He found that by moistening meat with gastric secretion he could prevent decomposition for many days, and that decomposing meat introduced into the stomach rapidly lost its putrefactive character and odour. Bunge [2] in 1890 was, however, the first definitely to express the opinion that the antiseptic action of hydrochloric acid in the gastric juice must be as important as its digestive function, and he instanced the fact that in a whole series of lower animals the commencement of the alimentary canal secretes a juice very rich in mineral acid, but containing no ferment and having no digestive action on the food. He observed that 0·2 to 0·3 per cent. of hydrochloric acid will render bouillon incapable of undergoing putrefaction, and remarked upon the coincidence that this was also the natural range of free acid strength in normal human gastric contents. Bunge also demonstrated important limits to the antiseptic power, certain organisms, especially those forming spores, being so resistant that exposure to gastric juice did not kill them. His examples were tubercle bacilli and anthrax spores. On the other hand, he noted that cholera vibrios were very easily killed by dilute hydrochloric acid, the result being well illustrated by Koch's [3] observation that it is possible to excite attacks resembling cholera in previously healthy animals only if their stomachs are washed out with sodium carbonate before the infected material is fed to them.

Nevertheless Bunge's teaching does not appear to have been reflected in practical therapeutics until relatively recent times. Various observers have reported successful reduction of intestinal infection if the gastric acidity has been reinforced by

oral administration of dilute hydrochloric acid. Armstrong,[4] for example, referred to alimentary toxæmia generally. Woodwark and Mackenzie Wallis [5] noted and remedied the deficient acidity in a series of rheumatoid arthritis cases associated with oral sepsis.

But much more striking clinical evidence concerning the remote effects of the absence of gastric hydrochloric acid has lately been brought forward by Hurst [6] in describing the achlorhydric gastric diathesis. Firstly, he points out that, although appendicitis and cholecystitis are probably always secondary to hæmatogenous infection, it being impossible to infect the appendix and gall-bladder via the lumen if the mucous membrane is intact and healthy, yet achylia gastrica may predispose to appendicitis or cholecystitis by permitting the access into the lumen of large numbers of pyogenic bacteria, which, once the mucous membrane has been damaged, maintain or aggravate the originally hæmatogenous infection. Secondly, with regard to rheumatoid arthritis, Hurst notes that a remarkably high proportion of those cases which show a definite intestinal focus of infection have also complete achlorhydria, and considers that in these people the gastric condition is evidently a powerful predisposing cause to bacterial invasion of the intestines.

Finally, in considering the relationship between Addison's anæmia and subacute combined degeneration of the cord, he draws attention to the constant association of oral sepsis and achlorhydria with these conditions, and, as evidenced by bacteriological examinations of the duodenal contents, to the presence of streptococci in the small intestines of such patients. He considers that through the activity of these bacteria, neurotoxic and hæmolytic poisons are produced, and shows that successful treatment must include, besides removal of all sources of infection, the oral administration of hydrochloric acid to repair the lost antiseptic power of the gastric juice.

Clinically the existence of this defence seems, therefore, to be established, but it is still undecided as to its full mechanism and as to which bacterial strains can most easily pass the gastric secretion. Therefore, taking advantage of the general adoption of the fractional method of gastric analysis and the possibility of obtaining duodenal contents by an Einhorn tube, I have attempted in these few experiments to determine in greater detail the nature and possible secondary effects of the gastric germicidal power.

Before quoting results, it will be well to point out that in every case power completely to kill bacteria has been estimated,

not that of merely inhibiting their growth. The time of experimental exposure to the acid has in most cases been twenty minutes and, although in a stomach which empties rapidly a small proportion of the swallowed bacteria may not be in contact with the acid juice for so long a time, the majority of them would be under its influence for considerably longer. Also it is to be remembered that the method of testing provides that practically *every* organism present has been killed before an end-point is given. Much shorter exposures to the same strengths of acid would have killed considerable numbers and impaired the vitality of many more. Though a portion of the swallowed material leave the stomach in less than twenty minutes, it is still submitted that the exposure times chosen provide a basis upon which satisfactory comparisons can be made.

Germicidal Power of Combined Hydrochloric Acid

Experiment 1.—As a preliminary experiment the effect of HCl in organic and in inorganic combination was noted.

The dilute acid was slowly added to milk, causing precipitation of caseinogen, and to nutrient broth previously inoculated with *B. typhosus* until protein combination was complete and free HCl detectable with Gunzberg's reagent. Samples taken meanwhile were incubated for twenty minutes, agar plates being poured at the start and finish and comparative bacterial counts made. No killing of bacteria could be detected until free HCl was definitely present in the original mixture. It appears, therefore, that the acid when in protein combination has no germicidal power.

Concerning inorganically combined HCl, Wright [7] proved, and the fact has been extensively used in the treatment of sepsis, that 2 per cent. saline solution will delay and 5 per cent. inhibit the growth of pyogenic bacteria, but that the organisms are not killed. I found, in fact, that even 25 per cent. sodium chloride did not kill a twelve-hour broth culture of *B. coli communis* in twenty minutes. Therefore it seems that the very much smaller amounts of inorganically combined HCl found in the gastric juice cannot have any appreciable lethal power towards bacteria.

Action of Free Hydrochloric Acid

Experiment 2.—To test the effect of free hydrochloric acid, a direct estimation of the germicidal power of dilute acid in normal saline solution was first made. Three or more strains

of each organism were tested in order to allow for minor variations of resistance among different strains.

To 5 c.c. of the various acid solutions were added 0·2 c.c. of a twenty-four-hour broth culture of the organism to be tested. After twenty minutes incubation at 37° C., 0·2 c.c. from each tube were removed and transferred to tubes of 5 c.c. of sterile nutrient broth. Incubation for forty-eight hours of these sub-cultures proved whether the organisms had been killed or not. It is to be remembered that had larger numbers of organisms been originally added to the acid, it would have been necessary to use slightly lower dilutions of HCl to obtain a lethal effect in the same time, but it is submitted that the quantities taken represent fairly what may be expected to occur in the case of swallowed bacteria, and that the end-points certainly represent the relative resistance possessed by the different groups of organisms.

The table which follows gives the average end-point for the organisms mentioned, a minus sign representing a completely lethal effect.

Organism Tested.	Percentage of Free HCl.											
	·005.	·01.	·02.	·03.	·05.	·075.	·1.	·15.	·2.	·3.	·4.	
B. subtilis	+	+	+	+	+	+	+	+	+	+	+	Group I.
B. anthracis	+	+	+	+	+	+	+	+	+	+	+	
B. coli communis	+	+	+	+	+	+	+	+	+	+	—	Group II.
B. coli Friedländer	+	+	+	+	+	+	+	+	+	+	—	
B. typhosus	+	+	+	+	+	+	+	—	—	—	—	Group III.
B. dysenteriæ	+	+	+	+	+	+	—	—	—	—	—	
Staphylococcus albus	+	+	+	+	+	+	+	+	—	—	—	
Staphylococcus aureus	+	+	+	+	+	+	+	—	—	—	—	
Streptococcus pyogenes longus	+	+	+	—	—	—	—	—	—	—	—	Group IV.
Streptococcus viridans	+	+	+	+	—	—	—	—	—	—	—	
Pneumococcus	+	+	—	—	—	—	—	—	—	—	—	
M. catarrhalis	+	+	+	+	—	—	—	—	—	—	—	
B. diphtheriæ	+	+	+	—	—	—	—	—	—	—	—	

It will be seen that according to their death-points the organisms appear to fall into four groups :—

1. Spore-bearing organisms which easily survive 0·3 per cent. or even stronger HCl.

2. Resistant strains of *B. coli* which are killed by about 0·3 to 0·4 per cent. HCl.
3. Bacilli of the typhoid-dysentery groups and the staphylococci which are killed by about 0·15 per cent. HCl.
4. Streptococci, diphtheria bacilli and other delicately growing organisms which are killed by 0·02 per cent. to 0·03 per cent. HCl.

To confirm the presence of a parallel action in actual gastric juice, the following modification was then made. The saline solution of the previous experiment was replaced by a markedly acid filtrate from a test-meal, which after six hours' incubation was found to be sterile and to have no peptic activity, and in which the free HCl had then been just neutralised with N/10NaOH. Small quantities of fresh HCl were then added to bring the free acid strength to the same levels as before. The bacterial death-points were determined as for the previous table. It will be seen that practically the same results were obtained :—

B. coli communis killed by 0·3 per cent. of HCl.
B. typhosus killed by 0·15 per cent. of HCl.
Streptococcus pyogenes killed by 0·03 per cent. of HCl.
Staphylococcus albus killed by 0·2 per cent. of HCl.

Peptic Activity

The free HCl in the gastric juice must therefore have a definitely selective as well as a general germicidal activity. The question remains, however, as to whether the peptic activity has of itself any germicidal powers comparable with those of the free acid. This point was tested as follows :—

Experiment 3.—To solutions of pure HCl in normal saline, soluble pepsin was added so that the resulting fluid contained 1 per cent. acid and approximately 0·2 per cent. pepsin. The solution was then incubated at 37° C. for three hours, after which it was found to be sterile owing to the germicidal effect of the free acid. The peptic activity of this solution as tested against egg albumen was found to be very marked. A series of dilutions was now made from this acid pepsin solution containing known amounts of free HCl and, using the same technique as before, the germicidal effect of these dilutions was tested, control tubes containing free HCl only being infected and incubated at the same time and under the same conditions. Typical strains of *B. coli*, *B. typhosus*, *Staphylococcus albus* and *Streptococcus pyogenes* were examined in

this way. With none of them could any appreciable increase of germicidal power be detected in the pepsin-containing tubes.

One may conclude, therefore, that compared with the action of free HCl, the peptic activity of the gastric juice has in this respect and over short periods no appreciable effect.

Effect of Organic Acids

It is now established [9] that no truly endogenous lactic acid is produced in the gastric contents when free HCl is present. Nevertheless in the absence of HCl, the effect of organic acid must be considered. For the experiment two organic acids have been chosen; lactic acid, because it is the only one which appears naturally in any quantity, and citric acid because its oral administration has been suggested [8] as a direct remedy for deficiency of HCl. It is to be remembered that the strength or H-ion concentration of these organic acids is much lower than that of HCl, *e. g.* a 0·15 per cent. solution of lactic or citric acid is approximately *p*H3, whereas HCl in the same dilution is *p*H1·5. Also in the gastric contents some or all of the organic acid may be in protein combination and, *vide* Experiment 1, germicidally inactive on that account.

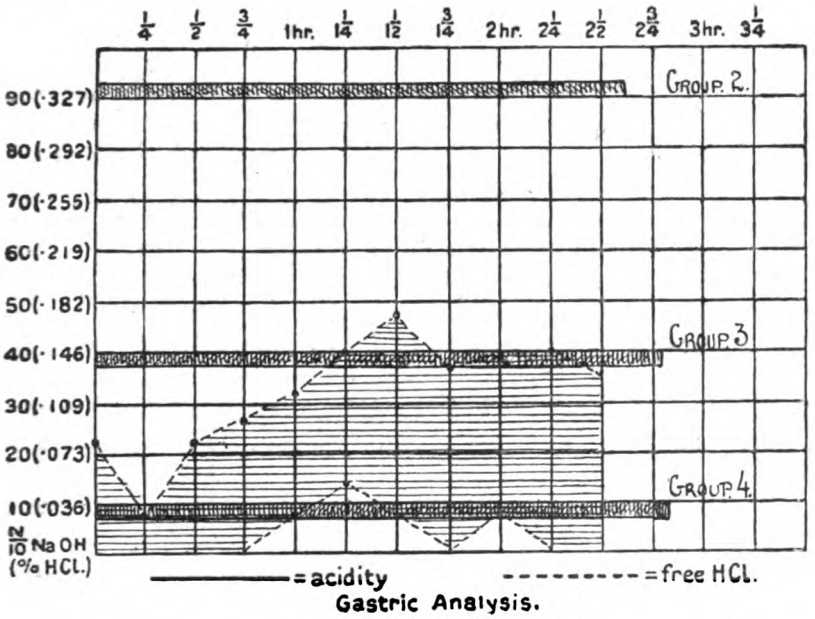
In practice Simon [9] found 0·4 per cent. lactic acid present on rare occasions in gastric carcinoma, but the usual maximum figure in instances of gastric fermentation is about 0·15 per cent. Tests have, therefore, been made with these acids in strengths of 0·4 per cent. to 0·1 per cent., using the same technique as in Experiment 2.

Experiment 4.—No lethal effect within thirty minutes' exposure could be detected in the case of any organisms except the most delicate strains. For example, no end-point was obtained with *B. coli*, staphylococci, streptococci of the viridans type, or air-borne organisms. One strain of *B. typhosus* was killed by 0·4 per cent., another survived it. Two examples of small colonied streptococci of the pyogenes longus type were killed by 0·3 per cent., which strength was also fatal to diphtheria bacilli. Citric acid acted similarly.

It might be concluded, therefore, that only if a considerable percentage of free lactic acid were present could any marked germicidal effect result. With the 0·15 per cent. of lactic acid usually obtained in fermenting gastric contents one could assume nothing more than an inhibitory effect upon delicate organisms while they remained in the stomach. Also, although in the processes of digestion citric acid may possibly help to make good HCl deficiency, its germicidal power, except when given in very large doses, must be negligible.

Results referred to the Average Gastric Cycle

The foregoing experiments indicate that, as far as the vigorous killing of bacteria is concerned, one need consider, in the gastric contents, only the percentage of free HCl. The various lethal strengths may be marked on a gastric analysis chart as below.



Gastric Analysis.

The shaded area represents the limits of free HCl in 80 per cent. of normal people.

The horizontal bands are drawn at the average free acid strengths which in 20 minutes are fatal to the three bacterial groups. Spore-bearing bacteria (Group I) are not affected by the 0·4 per cent. free HCl, and cannot be included above.

In reading the chart it is to be remembered that according as the actual exposure time in the living stomach is greater or less than that chosen for the experiment, the absolute lethal points should be somewhat lowered or raised. Nevertheless it is at once evident that swallowed spore-bearing bacteria and the more resistant coliform strains can readily survive passage through the average gastric juice. The more delicate organisms of the typhoid-dysentery groups and the staphylococci will survive only if the free hydrochloric acid tends to be low or the emptying of the stomach to be rapid. The streptococci, diphtheria bacilli, micrococci of the catarrhalis group and other readily killed organisms will leave the stomach in the living

state only if the free hydrochloric acid is extremely low or when a condition approaching achlorhydria exists.

Clinical Interpretation

These experimental results appear, therefore, definitely to be in accord with the opinions already quoted, that clinical conditions arising from intestinal infection with pathogenic organisms and absorption of their toxins may frequently arise from deficiency, temporary or permanent, of free HCl in the gastric secretion.

If, to remedy this deficiency, HCl be given by the mouth, it should be administered alone and not mixed with proteins such as those of milk, which immediately remove some or all of its germicidal power. Organic acids, such as citric acid, would appear to be incapable of making good the loss of germicidal power when the gastric juice is deficient in HCl.

The relative ease with which infection via the mouth occurs, especially in states of exhaustion, with members of the colityphoid group of organisms is illustrated in the foregoing diagram, the organisms successfully passing the gastric juice if the free HCl is relatively low. Also it appears that persons with a constantly high level of acidity would be the least liable to infection.

Since efficiency of the germicidal barrier appears to depend entirely upon the presence of ample free HCl, this barrier may be considered defective in all cases in which fractional gastric analysis shows low values for free HCl. In patients also showing active oral and pharyngeal sepsis the presence or absence of free gastric acidity must be of the greatest importance. It is suggested, therefore, that the oral bacteriological findings, the gastric analyses and the duodenal bacteriology be determined over a long series of cases. It may well be found that, whatever the cause of the acid deficiency, the presence of special strains of bacteria in the material swallowed would be attended with specific pathological results in those patients whose free HCl is constantly small in amount. With this object in view a case series has been started, and this it is hoped to analyse in full as the number increases.

Meanwhile it is submitted that the experiments outlined demonstrate the relatively simple mechanism of the gastric germicidal barrier, its specific power against the various common bacterial strains, and also that this barrier depends mainly, if not entirely, upon *free* HCl for its continued efficiency. The free HCl curve on a gastric analysis chart can, therefore, be taken as a direct indication of the germicidal power also.

My sincerest thanks are due to Dr. A. F. Hurst for his clinical suggestions and for allowing me the freest use of material from cases under his care, to Drs. J. F. Venables and T. W. Turner of New Lodge Clinic, and Dr. M. E. Shaw of Guy's Hospital, who have supplied me with many specimens and the result of chemical gastric analyses, and to the Clinical Research Association for placing at my disposal many laboratory facilities.

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SOME CASES FROM "CLINICAL"

JANUARY TO MARCH, 1923.

Physicians in Clinical:

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

Clinicals:

F. E. GRAHAM-BONNALIE.
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THE appointment of "Clinical"—or Clinical assistant in the two clinical wards at Guy's—is one of the oldest, if not the oldest, non-surgical clinical appointments in existence. Its origin is wrapped in obscurity, but it was certainly in existence over a hundred years ago, and most of the case histories quoted by Addison and Bright in their classical contributions to medical science were written by their Clinicals. The appointment is held by six senior students every three months, and the physicians and assistant physicians have always been in charge of the Clinical Wards in rotation, except for some months in 1842, when Bright, by arrangement with his colleagues and the Treasurer of the Hospital, was in continuous charge, in order that he might have greater opportunities for studying the association of albuminuria with œdema which he had recently discovered.

Cases of special interest are admitted into the Clinical Wards, which are consequently always a centre of active research. In the early volumes of the *Guy's Hospital Reports* short histories of interesting cases in Clinical were published with commentaries, and the following cases are recorded by the Clinicals of January to March, 1923, in the hope that this excellent custom, which has been allowed to lapse for over fifty years, will be revived.

A. F. H.

THREE CASES OF LEATHER-BOTTLE STOMACH

THE condition now commonly known as "leather-bottle stomach" was first described by Brinton in 1854 under the name of "cirrhosis of the stomach." Brinton regarded it as non-malignant, and due to inflammation of the "filamentous network of areolar tissue ensheathing the vessels" of the

stomach, and suggested the name "linitis plastica," which is still sometimes employed to describe this—"from the Homeric λίνον, *rete ex lino factum.*" He pointed out that the stomach is characterised post-mortem by failing to collapse by its own weight and by returning to its original shape after removal of pressure exerted on it, like a "caoutchouc bottle."

Since Brinton's time there has been much discussion as to whether leather-bottle stomach is a form of chronic gastritis or of cancer, but the latter view, which was first upheld in 1859 by Rokitansky, is now generally accepted, modern microscopical research having proved that it is a diffuse form of carcinoma.

All coats of the stomach are infiltrated with growth. Definite ulceration is rare, but superficial erosions, sufficient to lead to the constant presence of occult blood in the stools, are generally found. The surrounding structures are not often involved, and secondary deposits are rare except in lymphatic glands.

The following three cases were all diagnosed from the clinical history, the presence of an abdominal tumour, and the results of the x-ray and bio-chemical investigations. The two first were patients in Clinical; the third was a private case under observation at New Lodge Clinic during the same period.

CASE I.

By G. D. SHAW.

SYDNEY C., aged 33, a leather-worker, was admitted into Guy's Hospital on February 2, 1923, suffering from abdominal pain and vomiting. He had been subject to attacks of migraine since childhood. During the last two years he had had a feeling of fulness in the stomach after meals.

At the beginning of January 1923 pain developed, followed a few days later by vomiting. The pain was located behind the lower end of the sternum and occurred immediately after taking food; it was followed three hours later by pain in the right iliac fossa. A month later the pain became more persistent and lost all relation to food. It now started in the hypogastrium, and spread upwards to the epigastrium, being most severe in the latter position.

The patient usually vomited a small quantity of watery fluid in the early morning before taking food, but he also occasionally vomited directly after meals. His weight had fallen steadily, and he suffered from anorexia and constipation.

On examination he was found to have a palpable tumour, situated in the left hypochondrium and most readily felt on light palpation. The gastric condition was complicated by the presence of mitral stenosis, the result of a rheumatic infection at the age of twelve.

An x-ray examination showed the stomach to be small and tubular; no peristaltic waves were seen, but the meal passed with extreme rapidity through the patent pylorus into the duodenum, the appearance being quite characteristic of a leather-bottle stomach.

A fractional test-meal revealed complete achlorhydria with rapid emptying, and each fraction contained blood.

The fæces gave a strong positive guaiac reaction, and acid hæmatin and hæmatoporphyrin were found to be present.

A diagnosis of leather-bottle stomach was made from the x-ray appearance, associated with the presence of achlorhydria, blood in the gastric contents and fæces, and a palpable tumour. It was decided to make an attempt to perform gastrectomy. Mr. R. P. Rowlands, however, found that the stomach was firmly adherent to the surrounding structures; the walls were infiltrated with malignant growth, and the pancreas, mesentery and glands were also involved. Gastrectomy was thus clearly impossible, and nothing was done.

The patient died from exhaustion a fortnight later.

The autopsy revealed a typical leather-bottle stomach with areas of superficial ulceration in the mucosa. The whole organ was infiltrated with malignant growth, which had also invaded the pancreas. Metastases were found in the glands at the hilum of the liver and in the liver, spleen and pancreas. The mediastinal glands were involved, and the lungs were invaded along the bronchi.

CASE II.

By G. D. SHAW.

MARY H., aged 52, was admitted on February 25, 1923, for severe abdominal pain and vomiting. She had never had a day's illness until the onset of the present symptoms.

A year previously she noticed that she became tired more readily than formerly. In December 1922 she began to have pain behind the lower end of the sternum and in the epigastrium, which was accompanied by vomiting. The pain was severe, and occurred immediately after the ingestion of food; it was spasmodic in character, each spasm lasting for about ten minutes. The vomiting relieved the pain, and she was free from symptoms

until another meal was taken. Her weight had fallen from eleven to eight stone within a period of ten weeks. She was habitually constipated, and had passed no fæces for three days prior to admission.

On examination she was found to be much wasted, and the skin was sallow and pigmented in various places.

A tumour was detected by light palpation in the left hypochondrium; it was movable and of a tubular shape. From the history, and the shape and consistence of the stomach on pal-

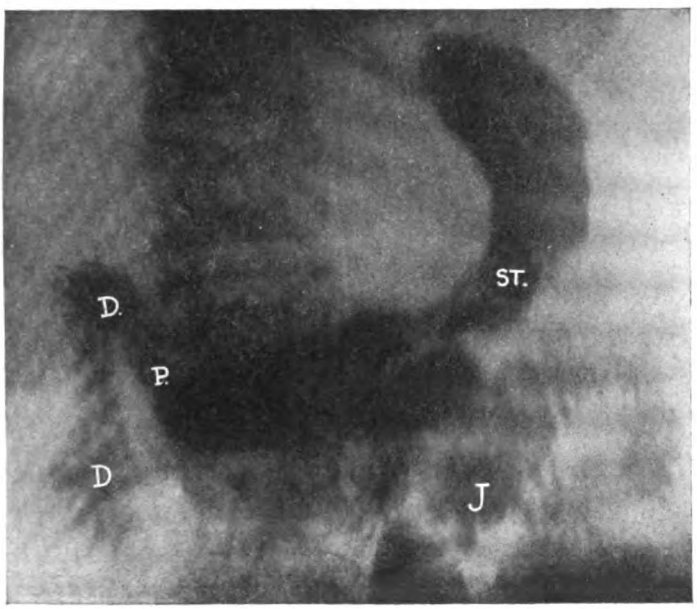

FIG. 1.

Case II.—Leather-bottle Stomach.

ST., small tube-like stomach; P., rigid pylorus; D., duodenum; J., jejunum.

pation, a provisional diagnosis of leather-bottle stomach was made. This was confirmed by subsequent investigations.

The x-ray examination showed that the stomach was high, tubular and small, and no peristaltic waves were seen, but evacuation was so rapid that the greater part of the opaque meal had reached the small intestines a minute after the meal was finished (Fig. 1).

It was found impossible to give a fractional test meal, as the patient was unable to swallow the tube, but figures suggestive of achlorhydria were obtained by estimating the basal metabolism before and after a meal, according to the method devised

by Bennett and Dodd. Examination of the fæces showed the presence of considerable quantities of occult blood.

In view of the experience gained in the previous case and the obvious debility of the patient, an operation was deemed inadvisable, and the patient was transferred one month after admission to the Fulham Cancer Hospital. During the time she was under observation, she experienced considerable pain and slowly lost weight.

She died ten days after her transfer. There was no post-mortem examination.

CASE III.

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

MRS. R., a woman aged 60, had suffered from indigestion for three months. Her general condition had hitherto been entirely satisfactory, and there was no history of any earlier gastro-intestinal disorder.

The onset was gradual. At first she merely noticed a progressive loss of appetite, associated with a feeling of nausea when food was taken. Later, a sensation of fulness was produced in the epigastrium by taking even the smallest quantity of food. Between meals no discomfort was experienced. Gradually the sensation of fulness was succeeded by actual pain, the onset of which always coincided with the taking of food. The pain, however, disappeared five minutes after the meal was finished. With the onset of pain the previous regular action of the bowels was succeeded by diarrhœa and increased intestinal flatulence.

Three months after the symptoms had commenced the patient had lost 15 lbs. in weight, and there was a further fall of 7 lbs. in the next ten days.

On examination she looked tired rather than ill, and she did not appear to be anæmic. The hæmoglobin percentage was actually 94.

Palpation of the abdomen revealed a horizontally situated tumour under the left hypochondrium, which could be rolled under the hand on deep inspiration. On rectal examination no secondary deposit could be felt in Douglas's pouch. The liver was not palpable and no enlarged glands could be detected. On x-ray examination the barium meal was seen to pursue a tortuous course through the stomach to the pylorus, through which it passed without any delay straight into the

duodenum, but no peristaltic waves were seen (Fig. 2). The appearance was suggestive of a tortuous tube with rigid walls. The entire meal had passed out of the stomach in less than half an hour.

A fractional test-meal showed complete absence of free hydrochloric acid with a low total of acidity. The stomach

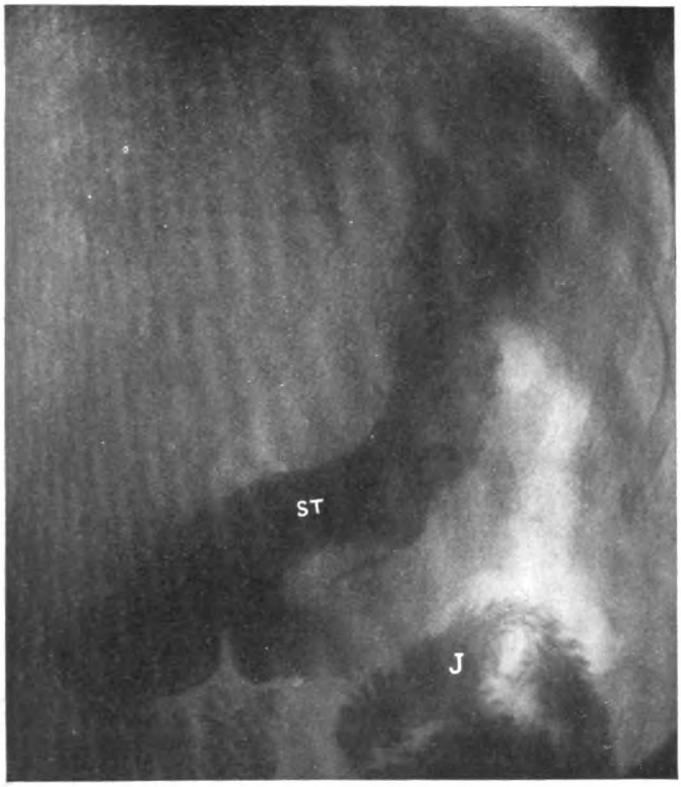

FIG. 2.

Case III.—Leather-bottle Stomach.
ST., small tube-like stomach; J., jejunum.

again emptied very rapidly, all traces of starch having disappeared at the end of one hour. Each fraction removed contained a small quantity of blood intimately mixed with the stomach contents. Both acid hæmatin and hæmatoporphyrin were present in the fæces whilst a farinaceous diet was being taken.

The Wassermann reaction of the blood was negative. The heart, lungs and urinary system were normal.

A diagnosis of carcinoma of the stomach of the "leather-

bottle" variety was made. As this type of cancer of the stomach is generally associated with complete absence of secondary deposits, the question of gastrectomy was discussed and at the patient's wish an operation was undertaken. A typical "leather-bottle stomach" was found and a complete gastrectomy was performed, part of the œsophagus and duodenum being also removed.

The patient died twelve hours after the operation.

The entire stomach was infiltrated through the whole thickness of its wall with growth, which ceased abruptly at the cardia and pylorus. Beyond these two points the mucous membrane was normal in appearance. The mucous membrane was thick and hard and there was no ulceration, the hæmorrhage having come from numerous minute erosions.

Symptoms and Diagnosis

The symptoms in the above three cases were very similar, and agree closely with those described by other writers on the subject. Pain under the lower end of the sternum or high in the epigastrium immediately after food, associated with nausea and often early vomiting, with anorexia and rapid emaciation, are almost always present. The pain, which may be accompanied by a distressing sense of fulness, often occurs even after a very small quantity of food has been eaten; this characteristic symptom is probably due to the diminished size and loss of elasticity of the stomach. The discomfort rapidly disappears, as the food passes so quickly into the duodenum. It is also relieved by vomiting. The rigidity of the stomach-wall makes it difficult to understand how this occurs, but Mr. G. D. Shaw makes the very plausible suggestion that the vomiting is due to reflux from the over-distended duodenum. The sausage-shaped, movable tumour in the left hypochondrium is also characteristic. Anæmia is not constant; the hæmoglobin percentage of 94 observed in one of our cases must be very exceptional in any form of cancer of the stomach.

In the two cases in which a fractional test-meal was given there was complete achlorhydria with low total acidity, caused no doubt by the actual destruction of the gastric glands by the widespread infiltration of growth. Evacuation was rapid in contrast with the delayed evacuation generally found in other forms of cancer of the stomach. Blood was present in each fraction, and the stools gave a positive guaiac test, and an acid hæmatin as well as hæmatoporphyrin spectrum; acid hæmatin is not often found in gastric cases, but may be

characteristic of leather-bottle stomach owing to the very rapid passage into the intestine.

The x-rays give a characteristic picture, which is quite pathognomonic. The stomach is high and small with a narrow tortuous lumen. No peristalsis occurs, but evacuation is nevertheless very rapid owing to the pylorus being completely incompetent, though rigid, as a result of infiltration. Five minutes after the opaque meal has been taken the stomach, duodenum and upper part of the ileum appear like a tube of uniform diameter with the barium equally distributed through them, and in half an hour the stomach may be empty.

The prognosis is almost hopeless. Though the diagnosis was made at once in all these cases, gastrectomy was only possible in one, and in that death occurred from shock a few hours later. If no operation is performed, death generally occurs between three and six months after the first appearance of serious symptoms.

A. F. H.

A CASE OF GASTRIC ULCER WITH HOUR-GLASS CONSTRICTION IN A MAN, CAUSED BY A BAND

By N. L. LLOYD.

HENRY A., aged 38, was admitted under Dr. Hurst on December 12, 1922, for epigastric pain and vomiting.

In 1918 he began to have slight pain in his epigastrium, the pain gradually increasing in intensity as months went by. It occurred with unfailing regularity about 1½ hours after food, being somewhat earlier after a small meal. He found that the pain disappeared almost immediately on taking food. Recently he sometimes vomited when the pain was present. In the week before admission he had vomited after every meal. He thought he had lost about a stone in weight in the last few months.

On admission the abdomen showed definite rigidity in the epigastrium, most marked on the left side. Pain was felt about two inches below the epigastrium, but most severe to the left of the mid-line. There was no cutaneous hyperæsthesia.

The x-rays showed the presence of a tender ulcer crater on the lesser curvature and an organic hour-glass constriction, which was not, however, sufficiently narrow to cause any stasis in the proximal segment of the stomach.

Examination of the fæces showed positive benzidine and guaiac reactions with a weak hæmatoporphyrin spectrum.

A fractional test-meal showed hyperchlorhydria with rapid evacuation.

Mr. L. Bromley operated on January 8, 1923. An ulcer was found high up on the lesser curvature. The hour-glass constriction was found to be caused by a fibrous band passing from the gastro-splenic ligament to the greater curvature and anterior surface of the stomach immediately below the ulcer. This constricting band was divided and removed, the hour-glass constriction being thus relieved. The ulcer was left untouched, and the abdominal wall closed. The patient made a rapid and uneventful recovery from the operation.

Following the operation he was given the usual hourly feeds, with olive oil, belladonna and large doses of alkalies. No more pain was experienced. On January 30 and the three following days an examination of fæces showed no occult blood.

On February 28 his stomach was again x-rayed. The hour-glass constriction seen on the first occasion had entirely disappeared, and the projection on the lesser curvature caused by the filling of the ulcer crater was considerably smaller.

His diet was now gradually increased, and on March 6 the x-rays showed no abnormality in the outline of his stomach.

He was discharged on March 7, having been free from all symptoms for over three weeks.

It was interesting to find that this case did not form an exception to the almost invariable rule that an hour-glass stomach caused by cicatrisation of a gastric ulcer, though not uncommon in women, hardly ever occurs in men. The fact that the surgeon left the ulcer to be treated medically after relieving the mechanical disability caused by the hour-glass constriction is a happy indication of the tendency of the present time to adopt medical treatment, which in this case was so successful, rather than submit the patient to the much more severe operation of partial gastrectomy, the after-results of which are by no means always satisfactory.

TWO CASES OF DIAPHRAGMATIC HERNIA *

1. DIAPHRAGMATIC HERNIA CAUSING PYLORIC OBSTRUCTION AND FATAL TETANY

By MAURICE MITMAN.

ARTHUR L., aged 54, a tramway employee, had for twelve years suffered from attacks of indigestion, which consisted mainly of bouts of severe vomiting and flatulence lasting for

* Case 2 was not in Clinical, but was under observation at New Lodge Clinic during the same period.

three or four days. During the attacks he could keep nothing down and became very constipated; between them he had slight pain located at the umbilicus. About five years ago he had a severe attack, during which he wasted considerably. He was treated as an out-patient and x-rayed. He himself declared that the x-ray report was negative, but no record of it could be found.

On January 18, 1923, he had an attack lasting a few days, and then, after an interval of another few days, a recurrence on January 27. The vomiting was so severe and intractable and the patient was becoming so emaciated that he was sent to hospital on the 29th, and was admitted at once. He was in an extremely feeble condition.

Nothing abnormal was detected on examination beyond an indefinite soft swelling in the left hypochondrium. During the examination he developed a carpo-pedal spasm with a typical "main d'accoucheur." Trousseau's sign was positive, but Chvostek's negative. About ten pints of dirty black fluid were evacuated from the stomach by a tube; the patient was greatly relieved and the abdominal swelling could no longer be felt. A diagnosis of pyloric obstruction with tetany was made. When a second attempt to pass a stomach tube was made, an unusual resistance was encountered in the lower part of the œsophagus. On January 30 it was decided to operate without a preliminary x-rays examination, as the patient was so weak, but he died during the following night.

At the autopsy a large, left-sided diaphragmatic hernia was discovered. The aperture, which was about the size of a half-crown and had a smooth margin, was situated in front of the aorta. There was a definite sac continuous with the peritoneum and pleura. The hernia contained the whole of the stomach and some omentum, there being old adhesions between these and the sac wall. The pylorus was situated at the orifice in the diaphragm, and the œsophagus opened into the upper and back part of the sac. The heart was pushed over to the right and the whole of the hernia was surrounded by lung substance.

It had been noticed during life that the maximum cardiac impulse was internal to its normal situation and the first mitral sound diminished in intensity, but these signs were attributed to emphysema.

2. DIAPHRAGMATIC HERNIA DIAGNOSED WITH THE X-RAYS

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

THE patient, a woman aged 60, had suffered for many years from epigastric discomfort immediately following each meal and lasting generally about two hours. During the last three or four years the symptoms had become more acute and she

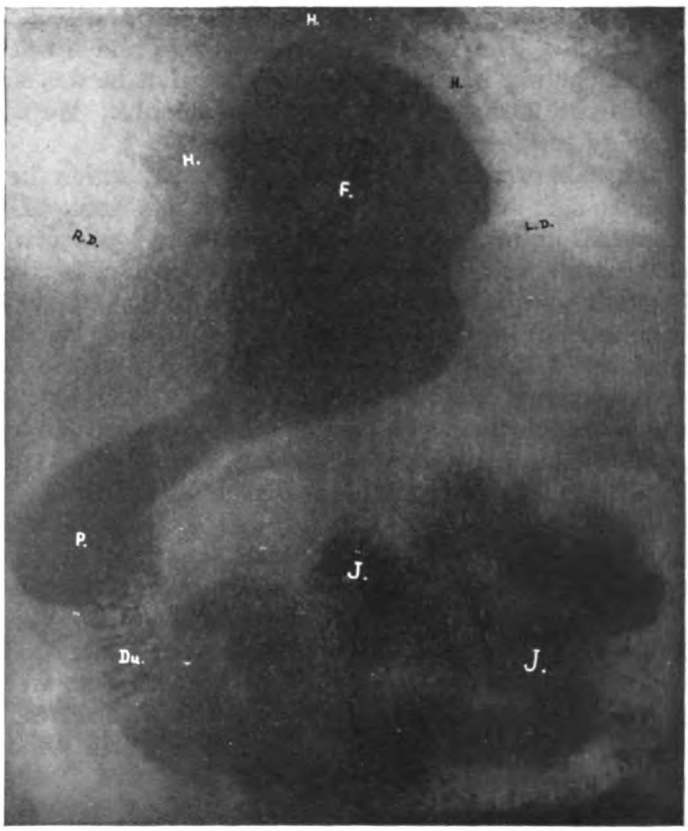

FIG. 3.

Diaphragmatic Hernia.

H., heart; L.D., left, and R.D., right dome of diaphragm; F., fundus of stomach; P., pyloric end of stomach; Du., duodenum; J., jejunum.

complained of epigastric pain, dyspnœa and flatulence. This increase in the severity of the symptoms coincided with a gradual gain in weight. When questioned closely as to the exact nature of her symptoms she stated that she experienced an increasing *sensation of fulness in the chest* whilst she was actually taking a meal; this sensation was always aggravated by lying

down, and was relieved by vomiting and by eructation. The dyspnœa occurred on exertion and on stooping and was always relieved by eructation.

Clinical examinations revealed no signs suggesting an organic origin for the symptoms.

A fractional test-meal was given, the tube being passed the normal distance. Each specimen obtained contained bile, and complete achlorhydria was present. An x-ray examination with a barium meal showed that a large portion of the stomach was in the thorax, posterior to the heart (Fig. 3). After the diagnosis of diaphragmatic hernia had been made as a result of the x-ray examination, a second test-meal was given, the tube being introduced a shorter distance. This gave a low normal curve of free acid, and bile was not present except in the resting juice. With the original meal there is little doubt that the tube was in the duodenum throughout the examination.

There was no history to suggest a traumatic origin for the condition, which was no doubt due to a congenitally large diaphragmatic aperture for the œsophagus. The patient's gradual increase in weight probably explains the aggravation of symptoms experienced during the last few years.

Commentary

By MAURICE MITMAN.

Diaphragmatic hernia is not a common condition and until recently was rarely diagnosed in life; it has even been missed during laparotomy. Recent progress in radiography has greatly facilitated the discovery of the condition, for the picture presented is pathognomonic, providing the hernia contains a hollow viscus. The condition may be congenital or acquired.

(i) *Congenital.*—This results from imperfect development of the diaphragm with consequent incomplete separation of the pleuro-peritoneal cavity into its two divisions. The left dome closes after the right; hence the greater frequency of the condition on the left side.

(ii) *Acquired.*—This is almost always traumatic. Many cases occurred during the war as a result of penetrating wounds of the diaphragm. In this variety the presence of the liver on the right side explains the greater frequency of left-sided hernia.

The commonest organs to herniate are the stomach, transverse colon and omentum, although any organ may be included. There is no definite symptom-complex, for so many varying

factors are concerned. Griffin gives three symptoms as present in a fair percentage of cases :—

(i) Pain in the epigastrium and chest immediately after eating.

(ii) Paroxysms of smothering without cause.

(iii) Vomiting without premonition.

It is interesting to note that in the first case only the last was present. In the second there was a striking history of an increasing sensation of fulness in the chest whilst actually taking a meal.

Symptom (ii) might be expanded to include the dyspnœa of the second case, which was caused by exertion and stooping and relieved by eructation. Other symptoms which may occur are :—

(iv) Excessive thirst and scanty secretion of urine in strangulation of the stomach.

(v) Displacement of the heart.

(vi) Borborygmi.

The fourth and fifth were observed in the first case, but their significance was not recognised.

Tetany in adults is most frequently due to pyloric obstruction with gastric dilatation. It was this fact that led to the seat of obstruction being assigned to the pylorus. Tetany was more frequent in former days, when carcinoma of the stomach was allowed to progress without palliative operation. The condition also occurs in parathyroid deficiency from any cause. This question and its relation to disturbance in calcium metabolism is discussed in the following commentary on a case of tetany after thyroidectomy.

A case of diaphragmatic hernia diagnosed on clinical grounds by Dr. Maurice Coburn, and confirmed by the x-rays, which was operated upon successfully, was recorded by Mr. R. P. Rowlands in these *Reports* in January 1921.

A CASE OF TETANY FOLLOWING THYROIDECTOMY

By N. L. LLOYD.

MARY U., aged 34, a secretary, had her thyroid gland removed for adenomata. The operation was performed in two stages with an interval of a year between, a portion of the isthmus being left behind.

A week after the second operation she had a sudden attack of respiratory distress, associated with painful spasms of her hands and feet, the limbs assuming the position usual in tetany.

Several attacks of short duration followed. There was no loss of consciousness. After a short time a different form of attack with definite loss of consciousness occurred; it was preceded by a sharp cry, the patient clenched her teeth and frothed a little at the mouth; she became very pale and her lips became blue; her limbs were rigid, but did not assume the position of tetany. Each of these attacks lasted about five minutes. On one occasion she fell down and struck her head. She had no recollection of these fits, but occasionally thought that "something had happened." On one occasion she volunteered after such a fit that she had had an excellent night's rest. The attacks of tetany had been preceded by a tingling sensation in the limbs, but the later type had no such warning.

At the same time her mentality changed completely; she realised that she did not recognise people whom she ought to know, but she was, if anything, rather amused thereby. She had formerly been of an irritable nature and self-willed, but she now became placid, easily pleased and very optimistic. Though of normal intelligence, she had a remarkably slow reaction time. Her memory for past and recent events was much impaired, the amount of impairment varying from hour to hour.

Chvostek's sign was well-marked, and Trousseau's sign was produced with a pressure on the arm of 70 mm. of mercury. A pressure of 60 mm. produced the tingling sensation, which usually preceded the tetany attacks, but it was insufficient to produce the spasm. Firm pressure on the median nerve, the radial pulse remaining undisturbed, was equally efficacious in producing the typical "main d'accoucheur."

She was under observation for three months, during which time estimations were made by Dr. Payne of the calcium content of her blood under varying treatment.

Date.	Treatment.	Calcium in mgrms. per 100 c.c. (normal average = 10·0).
18.3.23	Parathyroid, gr. 1/5, t.d.s.	4·0
3.4.23	None	4·3
12.4.23	Calcium lactate, gr. 15, t.d.s.	5·15
10.5.23	Calcium lactate, gr. 15, and dried thyroid gland, gr. 2½, t.d.s.	5·1

At the same time the calcium content of her urine was much diminished.

Her memory improved greatly as time went on, and after

having treatment first with dried parathyroid gland and calcium lactate by mouth, and finally with calcium lactate and dried thyroid gland (7½ grains per diem), she ceased to have any fits at all, her hair, which had been falling out since the operation, ceased to do so and began to grow again, and Chvostek's and Trousseau's signs, although still present, were far less easily demonstrated.

She was finally discharged after having been free from fits for a month.

Tetany appears to be directly dependent on diminished calcium in the blood. Recent work has shown that the calcium in the blood is remarkably constant in health, the normal being about 10 mgrms. per 100 c.c.; almost all of this is contained in the blood-serum. When the calcium content becomes less than 6·7 mgrms. per 100 c.c., signs of tetany appear, whether due to parathyroid deficiency, gastric stasis or rickets.

It appears impossible to reduce the figure below 4 mgrms. It is further found that of the 10 mgrms. normally present only 6 mgrms. are dialysable, and it has been suggested that the remaining 4 mgrms. are present in some combined form or in an ionic state, which cannot be eliminated, although it may be precipitated by ammonium oxalate.

MacCallum's view is that the parathyroid secretion controls the calcium metabolism and that the deficiency of calcium dependent on insufficient secretion results in an exaggerated nervous irritability, as shown by Chvostek's phenomenon.

It is interesting to recall a case described by Dr. A. F. Hurst in the *Reports* for 1910. A man had his thyroid gland removed for adenomatous change and three years later suddenly became depressed, nervous and extremely restless. He acquired an enormous appetite, but lost weight rapidly. His hair ceased to grow, although it did not fall out, and he no longer required to shave; at the same time he became quite impotent.

His nervousness and excitability were controlled for some time with opium, chloral and bromides, and he remained in much the same condition till three months later, when he commenced treatment with dried extract of parathyroid (Armour). From this moment he improved, progress being remarkably rapid. He put on weight, the tremor, nervousness and restlessness disappeared, and he was no longer impotent. It was, however, not for six months that his hair commenced to grow again. He is still well now, in the summer of 1923, and has only occasionally had to take parathyroid extract for short periods since his original illness in 1910.

A CASE OF SPONTANEOUS RUPTURE OF THE GALL BLADDER

By MAURICE MITMAN.

JOSIAH H., aged 64, an engineer, presented himself at hospital on March 10, 1923, because his friends had noticed that within the last ten days he had developed a yellow colour, which was increasing in intensity.

For the last six months he had been retching occasionally—usually, but not invariably, in the morning before breakfast. For six weeks he had had slight dyspepsia, which took the form of a mild aching pain in the lower part of the chest, associated sometimes with the retching and flatulence, and within the last two weeks infrequent vomiting had occurred, unrelated to meals. All these symptoms, however, had been quite slight. He had not lost weight and his appetite was good. He always had a tendency to constipation; his stools had become pale since the onset of the jaundice, and the urine dark.

On admission the patient, who was of a cheerful disposition, was well nourished. He was deeply jaundiced. The liver was much enlarged, the lower border crossing the middle line at the level of the umbilicus; it was of normal consistence and smoothness. The gall bladder was not palpable.

The urine contained bile pigment in considerable amounts, but no sugar. A fractional test-meal gave a normal curve; this was unexpected, as achlorhydria is generally present in severe pancreatic disease. The fæces were neutral and contained excess of soap crystals; stercobilin was present, but diminished in quantity.

Van den Bergh's test gave a well-marked positive direct reaction. The lævulose test showed no hepatic insufficiency. The Wassermann reaction was negative. The diastase index was 70 (normal 10–40), indicating the presence of some pancreatic disease.

A diagnosis of incomplete obstructive jaundice, the result of either chronic pancreatitis or carcinoma of the pancreas, was made.

Patient was so well that he was able to be up and about until March 19, when he developed slight pyrexia (99·2°) and was ordered to bed. On March 22 the temperature had reached 101·8°, but the patient felt just as fit as before, except for a little increase in the flatulence. The pyrexia was believed to indicate that an infection of the obstructed biliary passages was occurring, and the patient was urged to have an abdominal exploration,

and probably a cholecystenterostomy performed. He was very reluctant to have any operation and asked that the consultation with the surgeon be postponed for a few days so that he might discuss the matter with his wife. This was agreed to, and in the meantime treatment with hexamine was instituted.

On the afternoon of March 24, contrary to instructions, the patient stole out of bed to go to stool. As the lavatories were in use, he was compelled to wait for a time and as a result experienced some discomfort. Just as he was about to commence the act he was seized with abdominal pain, and collapsed. When put back to bed he was suffering from shock. The pain was not severe, but the abdomen was held rigid. He was seen a few hours later by a surgeon, who decided to watch him.

Next morning the rigidity had largely passed off, and there was no pain or tenderness. Some distension, however, had appeared, but no free fluid or peristalsis was detected. The bowels had not been opened, so an enema was given with a very small result. This contained no stercobilin, suggesting a more complete obstruction than before. During the day the distension increased, the liver dulness diminished and some vomiting occurred. A second enema was retained. A diagnosis of intestinal obstruction of a paralytic variety was made. An operation was now performed; the abdominal cavity was found full of bile and the intestines in a state of paralytic ileus. The gall-bladder had burst near the neck owing to weakening and sloughing of the wall as a result of infection secondary to obstruction. The head of the pancreas was very hard, and it was difficult to decide whether this was due to carcinoma or chronic inflammatory change. The gall-bladder was shrivelled, and not accessible for any anastomosing operation. The ducts were patent to the passage of a probe. A drainage tube was inserted down to the gall bladder area. The patient survived for nine days after the operation. A section of the pancreas obtained at the necropsy showed chronic pancreatitis.

Three points are of outstanding interest in this case :—

(i) The difficulty in deciding between chronic pancreatitis and carcinoma of the pancreas. Dr. Hurst has seen three cases diagnosed as the latter at operation turn out subsequently to be simple pancreatitis.

(ii) The exceedingly uncommon occurrence of a distended gall-bladder rupturing, except as a sequel of infection and ulceration secondary to gallstones. The extent to which the healthy gall-bladder may be stretched without giving way is truly remarkable; in fact it is probable that rupture never

occurs unless infection of the wall is present. It is interesting to note that in this case the gall-bladder was not palpable in life.

(iii) Some traumatism is usually the exciting factor in the production of a rupture in a distended and infected gall-bladder. In this case the precipitating factor was undoubtedly the straining at stool. I have been able to find records of only two such cases, one recorded by Willard in 1893, and the other by Lane [1] the following year. In the latter, however, only the mucous membrane was involved.

REFERENCE

[1] W. A. Lane: *Trans. Clin. Soc.*, xxviii. 160, 1894.

A CASE OF PNEUMOCOCCAL PERITONITIS ASSOCIATED WITH NEPHRITIS

By F. E. GRAHAM-BONNALIE, B.Ch.

IDA B., aged 9, was admitted on January 18, 1923, and died on February 28. Nothing was elicited as to her history, except that she had measles as an infant and a slight cough on and off for the last year.

Four days before admission her mother noticed puffiness of her face. On the next day she vomited and complained of headache, but was not drowsy. She had also pains in her legs and dyspnœa.

On admission the patient was thin and frail. There was œdema of the eyelids, lumbar region and ankles. The abdomen appeared to be slightly distended, and the urine contained 40 parts of albumen per 1000, but no other abnormal constituents were found. The temperature was 97·8°, pulse 92, and respiration rate 20. The breath sounds were impaired and râles were heard at both bases.

On January 25 the œdema had diminished, but the abdomen was more distended. There were no definite signs of free fluid.

On January 28 the abdomen was very distended; it was resonant except in the right flank. The patient vomited once. The bowels were opened normally. The next day the abdomen was still more distended and rather rigid. The child was in much pain, which was of a colicky nature. There was still no pyrexia. Mr. Bromley performed a laparotomy. Much loculated pus was found, and in the right flank a large collection of yellowish and almost odourless pus, which gave a pure growth of pneumococci.

On the next day the œdema of the face, back and ankles

had much increased and the patient was still in considerable pain.

On February 8 the wound broke down. An autogenous pneumococcal vaccine prepared from the pus was given. A swab was taken from the vagina, but no pneumococci were seen in a direct smear, nor were they grown on culture. The fæces grew only *B. coli* and a long chained streptococcus. On February 5 the patient's temperature rose to 100·4°—the first time it had been above 98·6°. The pulse rate was now 126.

On February 1 a white corpuscle count had showed 55,000 cells per cub. mm., mostly polymorphonuclear cells. On February 8 this had fallen to 45,000 and on February 23 to 20,000. The patient developed intractable diarrhœa and the wound continued to discharge pus, which became contaminated with *Streptococcus longus*. She died on February 28 from a terminal bronchopneumonia.

At the autopsy evidence of confluent bronchopneumonia was found at the left apex and base. Chronic generalised peritonitis was present with little signs of reaction. The kidneys were of the large white variety. There was no evidence of infection of the genital organs.

Commentary

This case presents many remarkable features. At the onset the nephritis was more obvious than the peritonitis. I have been unable to find anything in the literature regarding the association of nephritis with pneumococcal peritonitis. Presumably the former was also of pneumococcal origin, corresponding with the acute nephritis observed some years ago by Dr. A. F. Hurst in a case of pneumococcal empyema. The nephritis was unusual in that the only abnormal constituent of the urine was albumen, which at one time reached 4·8 per cent.

In all the cases of pneumococcal peritonitis which I found quoted in the literature there was a marked degree of pyrexia; in this case the temperature never rose above 98·6° until the twentieth day after the onset, when it rose to 100·4°. Diarrhœa is usually held to be a characteristic and early symptom of this form of peritonitis, but here again there was no diarrhœa until the late stages, and in spite of the low resistance and the degree of infection of the abdominal cavity, the bowels were opened normally once a day for the first three weeks.

There was no clue in this case as to the point of entry of the infection. There appear to be four possible modes of infection of the peritoneum by pneumococci—by the blood stream,

by spread from the intestines through the mucous membrane, by extension from the tonsil through the mediastinal lymphatics, and by the Fallopian tubes.

To not one of these can be definitely assigned the avenue of infection. Rischbieth [1] says, "Pneumoccocal peritonitis . . . is always secondary not to a single focus of disease but to a septicæmia. The view that the condition is secondary to pneumococcal septicæmia is the only one which meets all cases." As against this is the fact that the pneumococcus can rarely be found in the blood in the early stages. There is no direct evidence supporting the view that the infection comes from the intestine. Infection of the peritoneum viâ the tonsils and lymphatics can scarcely be credited, as the infection would have to spread in the opposite direction to the lymph flow and should give rise to massive lymphatic involvement, which is not the case. In one case pneumococci isolated from the abdominal cavity, vagina and blood stream were of Type I, whilst the pneumococci from the tonsil were of Type IV.

There appears to be more evidence in favour of infection occurring viâ the Fallopian tubes. According to MacCartney [2] the condition is almost entirely confined to the poorer classes, being uncommon in those who are well cared for, from which it is supposed that unkempt children are more liable to vaginal infection. Of 56 cases he collected from the literature 12 occurred in boys, and at post-mortems all these were considered to be secondary to a focus in the lungs; in 44 cases in girls, 8 were held to be secondary to the lungs and 36 were unaccounted for. Several cases are recorded where pneumococci could be isolated from the pelvic cavity, but not from the remainder of the abdominal cavity.

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[1] Rischbieth: *Quart. Jour. Med.*, iv. 205, 1910.
[2] MacCartney: *Brit. Journ. Surg.*, ix. 479, 1921.

NEPHRITIC ANURIA, LASTING SIX DAYS, WITHOUT URÆMIC SYMPTOMS; NEPHROTOMY; DEATH

By N. L. LLOYD.

MARY W., aged 20, single, was admitted under Dr. Hurst on February 23, 1923, for anuria. She gave a history of an illness eight years previously, which appears to have been scarlet fever, though some doubt was cast on this by the doctor who attended her. In June 1922 she noticed that her urine was darkly coloured, but she had no other symptoms and continued

at work. The colour of the urine became normal in about six weeks.

About three weeks before admission she began to feel rather sleepy, and a week later again passed dark-coloured urine. A fortnight later she vomited a little and was sent to bed. On February 19 she was menstruating, and her doctor examined a catheter specimen of urine, which he found to contain blood, albumen and a few casts.

Since the passage of the catheter she passed no urine at all, with the exception of about half an ounce the night before admission. The vomiting persisted, but was not severe, and she continued to feel somewhat sleepy. Apart from this she had no symptoms.

On admission she looked and felt well and behaved in a rational manner. Her body surface was hot and moist, and her complexion rather "muddy." Her tongue was slightly furred, and her breath was foul.

A catheter was passed, and about two drachms of thick urine was drawn off. This contained much albumen and blood, together with granular and blood casts, and a few pus cells.

Examination of the cardio-vascular, respiratory, alimentary and central nervous systems showed no abnormality. The systolic blood-pressure was 130 mm.

She passed a good night on February 23. The next day it was found that her blood-urea amounted to 4·2 parts per 1000, or 15 times the normal. Attempts were made to stimulate her kidneys by means of hot fomentations to her loins and colon douches, but without success. On February 25 she still felt very well, but passed no urine. She had no headache, twitching or other symptoms of uræmia, although she had now had almost complete anuria for six days.

A catheter was again passed and about a drachm of highly coloured urine, which contained much albumen and more blood, but no casts was obtained.

The diagnosis now lay between acute nephritis and obstructive anuria. The latter might possibly have been caused by a stone in each kidney, or by an aberrant vessel blocking the ureter of a single or horse-shoe kidney.

The patient was given a general anæsthetic; a cystoscopic examination showed normal ureteric orifices, of which one appeared to contract occasionally, although no urine was seen escaping. The kidneys were then exposed. They were found to be of normal consistence, though somewhat large. No obstruction could be found, and the pelvis was not dilated. The peri-renal tissue was in an œdematous condition. The

capsule of the left kidney was incised and some clear fluid, followed by blood, oozed out of the kidney substance. A drainage tube was passed through the kidney substance into the hilum and a second drainage tube into the peri-renal tissue. The incision was then closed.

The patient died eight hours later in a short convulsion, the only one she had throughout her illness.

The autopsy revealed nothing abnormal beyond acute nephritis.

MALIGNANT TERATO-BLASTOMA OF OVARY IN A GIRL OF FIFTEEN, SIMULATING TUBERCULOUS PERITONITIS

By G. D. SHAW.

ALICE P., aged 15, was admitted into hospital on January 22, 1923, for abdominal distension and pain. She was very well nourished, and did not look a tuberculous subject. Her family history was good and the patient herself had had no illness of importance.

The present complaint had begun early in the month with pain in the left hypogastrium, progressive enlargement of the abdomen, and dyspnœa on exertion. The pain was persistent, constant in position, and severe enough to waken the patient from sleep during the night.

On examination no abnormality was detected in the cardio-vascular, respiratory or nervous systems, and the urine was normal. The abdomen was found to be tense; a fluid thrill was readily elicited, and shifting dulness was well marked. Rectal examination revealed a fulness stretching from the cervix to the left pelvic wall, which was thought to be due to tuberculous salpingitis. The menstrual periods had commenced a year before the onset of symptoms; they had always been irregular, but were apparently normal.

After admission the pain assumed a shifting nature, one day being half-way between the umbilicus and xiphisternum, and at other times immediately below the costal margin on the right side.

A few days after admission 20 c.c. of fluid were withdrawn from the abdomen for diagnostic purposes. It was yellowish in colour, rich in protein. The deposit contained red blood corpuscles, leucocytes, of which polymorphonuclear cells and lymphocytes appeared in equal numbers, and some degenerate endothelial cells. Bacteriological cultures remained sterile.

One c.c. of the fluid was injected into a guinea-pig; it was killed six weeks later, but showed no evidence of tuberculous infection. A differential leucocyte count revealed no abnormality. The rectal temperature showed a difference of about one degree between morning and evening temperatures, and the pulse remained steady between 90 and 100.

The abdomen became progressively more enlarged. Three weeks after admission 14 pints of slightly blood-stained fluid were withdrawn. The patient, who had previously suffered much pain, was considerably relieved. On palpation a mass, resembling the rolled omentum of tuberculous peritonitis, was now felt stretching from the umbilicus towards the left costal margin. It was tender on deep pressure. A diagnosis of tuberculous peritonitis was made. A further paracentesis was performed three weeks later, and on this occasion 16½ pints were withdrawn. What appeared to be a glandular mass could be felt lying to the right and below the umbilicus. A further fortnight elapsed, during which time the girth of the abdomen at the level of the umbilicus steadily increased; the patient was then suddenly seized with acute pain in the right iliac fossa; the pulse became feeble and rapid, rising to 160, the temperature was slightly raised, and the tongue was dry and furred. Her appearance suggested an acute abdominal condition, and it was thought that acute appendicitis might have supervened. The muscles of the abdominal wall appeared to be slightly more rigid than before, the whole abdomen was dull on percussion, and the pain was increasing in severity, so immediate operation was decided upon.

A right paramedian incision was made; what appeared to be greatly thickened peritoneum was incised, and 15 pints of fluid were withdrawn. Further examination then revealed that the wall of a cyst springing from the left ovary had been opened. The pedicle was ligatured, and the cyst removed. It was found to weigh five pounds, and proliferating masses of tissue were growing from its inner wall and projecting into the cyst cavity. Dr. G. W. Nicholson reported that the tumour was a terato-blastoma, consisting of derivatives of all the germinal layers. The epiblast was represented by skin, tooth buds, Pacinian corpuscles, grey matter, glia and neuro-epithelial tubes, the hypoblast by respiratory and intestinal epithelium with a pylorus, and the mesoblast by areolar and fibrous tissue, plain muscle, erectile tissue, cartilage and bone. The neuro-epithelial elements in particular were slightly differentiated and in a state of active proliferation. The tumour was undoubtedly malignant.

The patient made an uneventful recovery and was discharged a fortnight after the operation. She was seen again on August 17, 1923, seven months after the operation. She was in splendid health. She had put on weight, her periods were regular, there was no evidence of ascites, and beyond slight tenderness over the scar the patient appeared to be normal in every respect.

The case is of exceptional interest in illustrating the difficulties which may in rare instances arise in the differential diagnosis of the ascitic form of tuberculous peritonitis from ovarian cyst. It recalls the historical case, in which Spencer Wells operated on what he believed to be an ovarian cyst, but which proved at operation to be tuberculous peritonitis. This error in diagnosis led to the subsequent introduction of laparotomy as a method of treating tuberculous peritonitis owing to the patient's unexpectedly rapid and complete recovery.

In the present case the appearance of robust health was a strong point against tuberculous peritonitis, but it is equally remarkable to find this in a rapidly growing malignant ovarian cyst. The cellular content of the fluid removed from the abdomen showed a smaller proportion of lymphocytes than is usual in tuberculous peritonitis, but it was certainly still less like what one would expect to find in a teratomatous cyst. Of more importance was the fact that dulness was always present between the pubes and umbilicus.

The shifting dulness in the flank is difficult to explain, but may have been caused by the whole tumour moving on its pedicle with the change of position of the patient. The masses felt after paracentesis and thought to be rolled omentum and glandular enlargement were the masses of growth found in the interior of the cyst.

FACTORS IN THE PREVENTION OF OPERATIVE MORTALITY IN EXOPHTHALMIC GOITRE

By E. G. SLESINGER, O.B.E., M.S., Assistant Surgeon, Guy's Hospital.

THE causation of exophthalmic goitre is by no means clear, and though several views have a considerable amount of evidence to support them, they remain as yet but theories. To whichever of these we incline, however, there remains the one outstanding fact that exophthalmic goitre is invariably associated with hyperplasia of the thyroid cells and that many of its symptoms are the result of excessive thyroid secretion. That the future treatment of this condition will in all probability be medical, or rather chemical, there can be little doubt, and equally little doubt that at present medical treatment is purely symptomatic and has little or no effect upon the course of the disease in itself.

Surgical treatment consists in removing a portion of the overactive thyroid gland with the object of cutting short the disease. It falls equally short of the ideal treatment in that it does nothing to remove the primary cause of the changes in the thyroid gland, and it results in a great amelioration rather than an actual cure of symptoms.

Surgery in exophthalmic goitre achieves, or attempts to achieve, a fourfold object. It saves life in a proportion of cases by cutting short a rapidly increasing intoxication which would otherwise lead to the death of the patient. Secondly, it materially lessens the severity of all the symptoms of the disease. Thirdly, by so doing, and by enabling the patient to gain in weight and in emotional control, it greatly lessens the period of invalidism. Lastly, in exophthalmic goitre, as well as the actual disturbances of the various systems which arise as a direct result of the disease, there occur a secondary series of changes which result from this disordered action, as, for example, myocardial changes as a result of the persistent tachycardia, and these secondary changes may be enough seriously to cripple the patient even when the actual disease has come to an end. By early surgical treatment these changes can be cut short or avoided, and this is a factor of great importance. The disadvantages of surgery are entirely those of mortality from the operation, and were there no risks in this respect, most

people with experience of the disease, both physician and surgeon, would agree that with our present limited knowledge surgery is the method of choice. Of recent years very considerable advances have been made in our understanding of the causes of surgical mortality in this disease, and as these causes become clear it is increasingly possible to avoid them.

The first and most important consideration from this point of view is

The Period of the Disease at which Operation is Undertaken

Exophthalmic goitre is, roughly speaking, a self-limiting disease. Certain very acute cases become rapidly worse and terminate in death within a few months, while, on the other hand, certain very mild cases become stationary within a few months of their onset and never develop the full symptom-complex at all. These, however, are the exceptions; the majority of cases, on the contrary, run a fairly definite course extending over a period of some four, five, or even six years. At the end of that time, though the activity of the condition is over, the patient is left with certain permanent changes of varying severity, which may or may not result in chronic invalidism, but which inevitably leave evidences of the previous disease.

During the period of its course the severity of exophthalmic goitre is by no means uniform, and, as Plummer has shown, it consists of a series of exacerbations of the intoxication known as crises. As a rule, from the onset, the symptoms increase steadily for a period of from eight to nine months, the height of the curve being marked by greater severity of all symptoms, and frequently by the onset of some, such as diarrhœa and vomiting, previously absent. After a varying period of weeks some improvement begins, and though the patient does not reach normal, she becomes markedly better. Loss of weight ceases and may be replaced by a gain, diarrhœa and vomiting stop, and the menses, which have usually stopped during or just after the crisis, may appear again. This improvement almost invariably follows the crisis, and as the increase of symptoms which precedes the crisis will frequently lead to the trial of new remedies, it must be discounted in considering their effects. Further crises with subsequent improvement occur during the course of the disease and at varying intervals. They are usually less severe than the first one, but each leaves the patient's general condition a little worse than it was before. Gradually as the disease dies out the severity of the symptoms diminishes, but

the patient still retains certain definite pathological changes, such, for example, as exophthalmos and cardiac muscle damage, as evidences of the storms through which she has passed.

Operation should hardly ever be undertaken during a crisis, as it is then that fatalities are most likely to occur. The treatment during the crises must be medical and symptomatic, and operation should be postponed until all symptoms are well on the down grade. Arbitrarily it is wise to refuse to operate within two months of the maximum severity of symptoms. It is unfortunately the case that the surgeon is very frequently asked to see the case at the period of crisis. The increasing severity of symptoms induces distrust of the medical measures which are being employed and the surgeon is called in as an alternative. Nevertheless, except in very exceptional cases, safety lies in waiting, and in this disease of all others it is the surgeon who must accept the responsibility of deciding *when* operation is to take place. During the first few months of the disease operation is seldom indicated, because there is no method of telling what the severity of the attack is going to be, and when a moderate degree of severity only has been reached symptoms may recede and not again become severe. In such a case operation is, of course, not indicated. On the other hand, in face of a steady increase in severity, the sooner within reason that operation is carried out, the shorter will be the duration of the illness and the less will be the permanent effects. Diarrhœa, vomiting, and rapid loss of weight definitely contra-indicate operation, since they indicate the near approach of a crisis and should lead to medical treatment for a time until the danger period is passed.

On the other hand, the most favourable single indication of safety is the reappearance of the menses after a varying period of amenorrhœa. Amenorrhœa is a far more frequent result of severe exophthalmic goitre than is generally taught, and in my opinion the reappearance of the menses in these cases is of the utmost prognostic significance. The most usual time for the patient to come to the surgeon is at or about the period of the first crisis. Hence it is important to take a careful review of the history and to treat the case long enough to secure a proper orientation of the stage of the disease which is being dealt with and to delay operation until at least two months from the time of maximum severity of symptoms, if the first crisis is found already to have occurred. In regard then to the *time* of operation the points to be borne in mind are:

1. As a rule not to operate within the first six months.

2. Not to operate within two months of a crisis.

3. To choose the down grade of severity of symptoms, rather than the up grade, if possible.

4. Always to have a clear perception of what stage in the disease the particular patient has reached.

What Operation should be Performed

Next in importance after when to operate, comes the question of what is to be done. This latter is of great moment not only in regard to mortality, but equally so in regard to the results to be obtained. Many so-called surgical failures are cases in which not enough has been done, cases which Kocher described as " nicht fertig operiert," and consequently it is not fair to put blame on the surgical principle which properly attaches to the detail of technique.

Generally speaking it can be said that in a chronic case of moderate severity it is not enough to remove one lobe or one lobe and isthmus only, and if the highest measure of improvement is to be obtained, at least three-fourths of the total gland tissue should be removed.

In considering the surgical plan to be followed with any particular patient the probable post-operative reaction must be visualised and compared with the existing severity of symptoms. If it appears possible that the severity of the reaction may carry the patient over the border line of safety, a stage operation is advisable. This will be used in most of the severe cases. The stage operation will consist either of two partial thyroidectomies at intervals, or a single or double or even two single ligatures followed by thyroidectomy. The reaction to a single ligature, which can be done in bed under local anæsthesia, is a most valuable guide to the probable behaviour of the patient after a subsequent thyroidectomy and should always be employed in cases of doubt. If a ligature is performed, it should be a ligature of the upper pole of the gland rather than the superior thyroid artery itself, as the inclusion of the sympathetic filaments passing to the gland probably affects the result to a considerable degree. In a large number of cases it will be found safe to perform partial thyroidectomy limited to one lobe at the first operation, and to remove a portion of the other lobe subsequently. Such a decision will depend partly on the severity of symptoms and partly on the ease and speed of the operation and the amount of blood lost. In cases of doubt it is far better to do too little at the first operation than too much. In the less severe cases and those operated on early in the

disease a one-stage operation is frequently safe and advisable. It is an interesting fact that the improvement after the first operation is usually so marked and the discomforts are so small that patients rarely withhold consent to the second procedure. It must be emphasised that ligature of one or even two poles of the gland is practically never by itself sufficient. Its advantages, however, are that it provides a guide to the probable degree of reaction in a given case, that it will improve a bad patient sufficiently for thyroidectomy to be safe, that it is of great value if doubt exists as to the period of the disease in relation to the crisis, and lastly it is of value in that its simplicity and painlessness take away the patient's fear of the more severe subsequent procedure. If this little operation were performed more frequently as a preliminary, many of the post-operative deaths in bad cases would undoubtedly be avoided.

Cardiac dilatation in exophthalmic goitre patients is of grave significance, and it has been well pointed out by C. H. Mayo that " dilatation which exceeds one inch is a serious condition, while that of an inch and a half will give a percentage of unavoidable mortality for the radical operation of thyroidectomy." Such patients should be treated medically for a time, and then should have a single ligature performed in bed with local anæsthesia as a preliminary measure. The closest co-operation between physician and surgeon is needed in these cases, and nowhere is such co-operation more fruitful.

Operative Technique

Certain questions of technique also in operations on exophthalmic goitre cases are of importance from the point of view of mortality prevention. First and foremost of these is the amount of bleeding. These patients stand loss of blood very badly indeed, and every care must be taken to avoid it. As many vessels as possible should be secured before they are cut, and it will usually be found easier and surer to secure bleeding points by quickly underpinning with a needle and catgut than by the method of forceps and ligature. Bleeding is especially severe in those recurrent cases, in which the portion of gland left after operation has enlarged with recurrence of symptoms. My only death, so far, following thyroidectomy, occurred in such a case from failure to appreciate this fact.

The other technical point of importance is gentleness in handling. In my opinion the chief advantage of local anæsthesia is the gentleness it forces on the operator. Adequate exposure by free division of the pre-tracheal muscles, and the

use of the knife in preference to blunt dissection wherever possible, are the most important aids in this respect. The infusion of large quantities of saline subcutaneously before and during the operation does much to lessen post-operative reaction. This is probably because it tends to reverse the flow in the lymphatics, fluid being excreted from the wound surface rather than absorbed from it.

Walton has recently drawn attention to the greater mortality after operation in exophthalmic goitre in the three hot months of June, July, and August (*Brit. Med. Journ.*, June 23, 1923), and finds a mortality of 20 per cent. during these three months as compared with one of 5 per cent. for the whole year. Exophthalmic goitre patients sweat excessively under any conditions, and particularly during operations, and it would appear possible that excessive loss of fluid is the explanation of the interesting fact pointed out. It is at any rate certain that infusion with four to six pints of saline is of the greatest possible value in combating hyperthyroidism.

Morphine should be administered freely, and quinine hydrobromide by mouth or rectum is of value for the first two or three days after operation.

Crile's practice, in cases of bilateral thyroidectomy at one sitting, of giving a little thyroid for a time is valuable in giving the body time to adjust itself to its new conditions.

Anæsthesia

The anæsthetic question has long been a matter of controversy, and there is little doubt that in the past much responsibility for fatalities has been put on the anæsthetists which properly attached to the surgeon. Most workers are agreed that *chloroform* is a poison to these patients and *should never be used under any conditions.* Intratracheal ether, which of recent years has been advocated, is in my opinion contraindicated, firstly because the depth of anæsthesia required to pass the intratracheal tube exposes the patient to unnecessary risks, and secondly because the operator is apt to deal unknowingly roughly with the trachea, being deprived of the warning which ordinary anæsthetisation permits. In my opinion the choice is between open warm ether and local anæsthesia. The latter has advantages in allowing co-operation by the patient and in forcing the necessary gentleness of handling on the operator. On the other hand, the mental upset entailed by the knowledge of the operation and the additional time required appear grave disadvantages.

Light ether, or better, ethanesal, anæsthesia gives every satisfaction and in expert hands appears to me the anæsthetic of choice.

Finally, it cannot be over-emphasised that the psychology of these patients has a great bearing on the result. Far better results and a far better post-operative course follow in patients who are convinced beforehand of the beneficial results of surgery. Such a frame of mind should be deliberately induced in these cases, as can easily be done by suggestion during the preliminary period of treatment, so that operation, when it comes, seems to come at the earnest desire of the patient, who under those conditions suggests to herself a feeling of safety which has a definite bearing on the realities of the situation.

Conclusions

The factors tending to prevent mortality after operation for exophthalmic goitre are :

1. Not to operate in the first six months.
2. Not to operate near a crisis of symptoms.
3. Not to operate while diarrhœa and vomiting are present, or during rapid loss of weight.
4. In cases of doubt and in severe cases to do a preliminary ligature.
5. Medical treatment followed by a preliminary ligature is indicated in the presence of cardiac dilatation.
6. To perform a stage operation in all severe cases.
7. The avoidance of excessive bleeding.
8. Gentleness in handling.
9. Massive saline infusion and avoiding operation in very hot weather.
10. Avoiding chloroform in any form, and any deep anæsthetisation.
11. Preliminary psychotherapy.

THE CAUSATION OF CATARACT

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In considering the ultimate cause of cataract, a point on which final agreement has never been reached, I shall limit my survey on this occasion to the following lines of thought :—

(1) that the process started by " needling " or discission of the lens is one of digestion;
(2) that hitherto sufficient attention has not been paid to the resistance of the cell membrane of the lens fibres in the maintenance of the normal pellucid condition;
(3) that cataract may be the result of a ferment reaching the lens fibres and starting a digestive process.

The crystalline lens is a mass of protoplasm enclosed in a capsule and suspended by fibres in the posterior chamber of the eye, immediately behind the pupil. It is without blood-vessels or nerve fibres, and growth is maintained throughout life by means of the deposition of fresh fibres on its external surface; the central fibres are in consequence among the oldest in the body, as they are laid down before birth and remain *in situ* throughout life. It must be remembered that the lens tissue, particularly that portion of it situated in the centre, is remote from all external influences so far as direct contact with nutritional sources is concerned, and its metabolism must of necessity be extremely slight. The cortical part has more vitality, and it is here that growth takes place and pathological changes usually appear first; the centre of the lens seems to be barely alive, and all influences, whether nutritional or pathological, must be very slow in effecting any change. It could only be through the aqueous fluid that anything which might act on the lens would reach it, so that in connection with the nutrition and pathology of the lens we have the following factors to consider :—

(1) the composition of the blood;
(2) the condition of the epithelium of the ciliary body;
(3) the aqueous fluid;
(4) the capsule and its epithelial lining; and
(5) the cell membrane of the lens fibres.

The chief characteristic of the lens is its wonderful transparency, and it is interesting that this is not lost as a result of any so-called senile change, its clarity being generally maintained unimpaired throughout life, even to extreme old age. The capsule, which is a product of the embryonic cells of the lens vesicle, differs in chemical composition from the natural lens cells, being of ectodermic origin, and reacting to digestive processes in a manner similar to ectodermic structures.

Mlle. Toufesco,[1] who has examined the capsule with considerable care, describes three different kinds of cells lining its anterior part :—

(1) large clear central cells with intercellular bridges;
(2) smaller peripheral cells; and
(3) equatorial cells forming fibres by which the lens grows.

As in fœtal life these cells are nourished by a real blood system, we may assume that they are of primary importance as regards the growth and nutrition of the lens, at any rate at that time; this important function is probably retained throughout life, although not with the same completeness after birth. It is evident that the lens must receive nourishment, for it has two functions to fulfil, to remain transparent and to grow.

The question of the nutrition of the crystalline lens is closely allied to the question of the nutrition of the living cell, and when the one problem is solved the other probably will be also. The chemical constitution of the normal lens is approximately : water 63·5 per cent., and solids 36·5 per cent., of which proteins account for 35 per cent., and lecithin, cholestrin, fats and salts, the small remainder. The proteins are abundant, and consist for the most part of serum-globulins and a serum-albumin. Apparently the lens-albumin has a specific action, and differs biologically from all other albumins in the human body. The salts of which the normal lens contains traces are potassium, sodium, calcium, and magnesium, and in India it is said to contain silicon also, but this does not appear to be so among Europeans.

The cataractous lens shows the following changes : the weight and volume are diminished, in the later stages there is less water and the potassium salts are reduced, whilst the calcium, magnesium and sodium are increased in proportion, the potassium salts and water apparently passing out through the capsule. The cataractous lens is more nearly allied to the composition of the blood and lymph; it does not show evidence of senile changes, but rather a moribund condition; in other

words, the cataractous lens is a dying or dead one. Burdon Cooper [2] has demonstrated the presence of leucin and tyrosin, which are products of protein digestion, in the aqueous and in the cataractous lens itself. Cystin and an increase in cholestrin have also been found, and Roemer [3] states that the aqueous contains a sugar-producing ferment.

In the course of clinical ophthalmic surgery it is often necessary to produce a cataractous condition of the lens preparatory to ensuring its solution. This is called "needling," and is done by deliberately opening the capsule of the lens and allowing the aqueous humour to have free access to the lens substance, which eventually becomes opaque, dissolves and disappears. The lens proteins are hygroscopic; this may be because of the lens albumin itself or because of its structure, consisting as it does of bundles of fibres massed together which would act, as thin glass plates do, in producing capillary action. We must assume then that a transparent healthy lens has an intact capsule and that the completeness of the capsule is essential for clarity.

The changes taking place in the lens in cataract are of the nature of hydrolysis—a definite decomposition, in which the protein of the lens is made to assimilate the constituents of a molecule of water and then breaks down into one or more simpler substances. The essential point is that it is a definite decomposition; the products are quite dissimilar to the parent substance, and the process is of the same type as digestion. In hydration the process is quite different; water is merely tacked on to the parent substance without undergoing any change.

Enzymes bring about hydrolysis, and the majority add or remove the elements of water and from this aspect of their activity are called hydrolysing. In the operation of discission of the lens an enzyme gains access to the protoplasm.

Cannot we then conclude that the process started by discission or needling of the lens capsule is one of digestion of protoplasm brought about by the presence of a ferment starting a hydrolytic reaction exactly similar to the digestive process carried on by amœba or other unicellular organisms, and resulting in the breaking down of the complex protein molecule into simpler ones, as is customary in protein digestion? If that is the case we must emphasise the fact that the presence of the lens capsule and its effective resistance to the ferment present in the aqueous seem necessary to prevent these changes occurring in the lens under normal conditions. Although the lens capsule when broken allows cataract to form, it is also true that the

lens will remain transparent without its capsule for a limited time. This suggests that the capsule, though a barrier to the entry of noxious substances to the lens fibres, is not the only one; possibly another and a more delicate one exists. As a result of an injury, damage may be done not only to the lens capsule but to the lens fibres also, and direct damage to the lens fibres would break down the second resistance, which we must now consider.

The lens, as has already been pointed out, lies isolated in the aqueous, and neither filtration, osmosis nor secretion alone accounts for its nutrition, but very little attention has been paid to the question of the resistance of the parenchymatous cells of the lens itself. Probably every living cell has a specific resistance of its own. The surface of contact between two liquids that will not mix is always the seat of a special kind of energy, as at the interface are electrical forces and a higher concentration of the dissolved substances than exists in the body of the liquids, and these forces play an important part in physiological phenomena. It is quite clear that the molecules which make up the outer surface of any mass are exposed to influences differing from those in the interior, the two most striking being surface tension and electrical changes.

In the case of two liquids there is also a condensation or higher concentration of the solute at the interface than in the body, and, according to Ramsden,[4] proteins can and do concentrate to form cell membranes or some portion of them. Pfeffer, Naegeli [5] and others have found that a new film may be formed by this means when the protoplasm of cells is broken up, and this film is supposed to be produced by the surface condensation of some of the constituents of the cell protoplasm. Hence solid particles sufficiently large to be microscopically visible might pass through the cell membrane by breaking it, the membrane being reformed behind after particles have passed through. This would explain the phenomenon of phagocytosis. Substances in the ionic or colloidal state would, however, require pores by means of which they might permeate the membrane, but as far as we have any evidence these do not exist in the lens capsule. As most of the enzymes of the body are in a colloidal state, their action is exerted on the surface of the interphase. From this we may argue that the lens fibres and cell membrane of the lens cells themselves, and not alone the capsule, resist the digestive action of the aqueous; aqueous can pass within the capsule and traverse the lens by means of the intercellular path, provided the enzyme present in the aqueous is prevented entering through the capsule; when,

however, this defence fails, there is still another in the cell membrane.

It is difficult to determine what is the exact nature of the process by means of which the lens is nourished. Neither osmosis, secretion, filtration, nor imbibition seems to explain all the facts. Filtration is unlikely, as there are no pores, channels, or openings in the capsule, and the intracapsular pressure is above that of the aqueous surrounding it. Simple osmosis is also not a satisfactory explanation, as the aqueous humour and the capsular contents never amalgamate, but in all probability osmosis does take place between the aqueous and the intercellular cement substance, and is limited by the cell-membrane. Secretion undoubtedly plays a part in the nutrition of the lens, as, of course, the composition of the aqueous itself is controlled by the selective activity of the cells of the ciliary body, and the epithelium of the capsule also has some power over what passes into the lens substance; imbibition or diffusion probably contributes a part as well.

The cells of the ciliary body are natural and effective filters allowing certain particles of the blood stream to pass through and form the aqueous humour, which in turn permeates the vitreous humour. It seems to me that it is not the capsule of the lens that prevents the aqueous humour from reaching the intercellular cement substance between the lens fibres, but that it is the cell membrane of the lens fibres themselves which forms a barrier to the actual entry of the aqueous humour into the parenchymatous fibres, as the lens fibres may remain clear and transparent though the lens capsule is removed, at least for a limited time. Primary cataract, therefore, is probably due to the cell membrane failing to prevent the entrance of noxious material into the substance of the fibres themselves.

There are then three positions where the defence may be broken down: (1) the cells of the ciliary body; (2) the capsule of the lens; and (3) the cell membrane itself. It would thus occur in the cells of the ciliary body after iritis and cyclitis when secondary cataract supervenes; in the capsule of the lens after traumatism and in gross defects in the capsule itself; and in the cell membrane in a more subtle and slow process culminating in the condition of primary cataract.

Recent writers seem to me to have paid too little attention to the existence of the cell membrane which covers the surface of living cells, and which is of importance as regulating the permeability and osmotic pressure of the cell. It has been contended that the intra-vitam protective mechanism against osmotic changes must lie in the capsule and its epithelium, and

probably it does to a certain extent, but the cell membrane must not be forgotten and is in all probability the more important factor. The cell membrane is semi-permeable—that is to say, it allows water to pass but holds back dissolved substances—and this permeability of the membrane is not always constant.

If now we turn to the clinical side of the question and consider the various diseases and conditions with which cataract is associated, the following is a more or less complete classification.

(1) Hereditary—familial and congenital cataracts.
(2) Lamellar cataracts (these occur in early life).
(3) Cataract associated with certain so-called "deficiency diseases."
(4) Cataract due to poisons.
(5) Cataract associated with general diseases.
(6) Traumatic cataract.
(7) Senile cataract.

(1, 2, 3) *Familial and Congenital Cataract*

The occurrence of cataract either in several members or in several generations of the same family, or at birth, suggests two points, either of which might conceivably be the cause: (1) an inherited toxic agent, with regard to which I shall have more to say when speaking of poisons as a cause of cataract; and (2) an inherited defect in the development of the lens and its capsule. That children may be born with opaque lenses is beyond question, and the researches of Treacher Collins [6] and others have proved by definite microscopical evidence that a defect of the capsule is sometimes the cause. Collins concludes that "lamellar cataract is not a clinical entity in the way of disease, but a form of opacity of the lens which may be brought about by different causes, the essential factor for its production being a temporary disturbance in the nutrition of the lens, ending abruptly, and followed by a period of normal growth." This does not suggest what is the cause of the temporary disturbance, but only notes that it acts for a limited period; and no unanimous conclusion on the subject of causation has been arrived at.

The association of cataract with certain deficiency diseases is a wide one; I refer to diseases which have been attributed to defects in the internal secretion of the ductless glands, such as cretinism and tetany, to vitamin deficiency as in rickets, and to some unknown condition as in mongolism and myotonia atrophica. But it must be confessed that so little is known

regarding the origin of the two last-named diseases that to argue regarding the etiology of cataract from them is to argue from one unknown to another. In the others, however, it is probable that deficiency of the internal secretions of the ductless glands (or of vitamins) is responsible for the very varied symptoms present. A degeneration of the capsular epithelium might occur, caused by deficient internal secretions or vitamins.

(4) *Poisons*

It is obvious that the toxins of various micro-organisms present in the eye or even in remote parts of the body may gain access to the aqueous humour and directly poison the lens, and this hypothesis has suggested those prophylactic measures associated with the treatment of early lens opacities, whereby it has been sought to retard their development by scrupulous attention to oral, nasal, intestinal or other possible sources of sepsis. But over and beyond this we have knowledge that various substances can and do poison the lens and produce cataract with unerring regularity. If naphthalin dissolved in liquid paraffin is introduced into the stomach of a rabbit a cataract develops very similar to the ordinary spontaneous cataract occurring in man. It is some derivative of the naphthalin that passing through the intestinal tract produces it, as lenses placed in naphthalin do not turn opaque. If the dose is small the lens may recover its normal transparency, but if sufficiently large a permanent opacity is produced. Pagenstecher [7] has published the results of experiments on pregnant rabbits and guinea-pigs fed on naphthalin, showing that not only cataracts but also various congenital malformations can be produced by this means. This all goes to prove that toxic agents influence the development of the lens, and not only the lens, but also the cells forming the iris, choroid, conjunctiva, cornea and lids. The poison of bee-stings introduced into the anterior chamber causes definite lens opacities in the pupillary area under the capsular epithelium. Many other substances capable of producing lens opacities are known, such as ergot, grape sugar, menthol, nitrate of soda, etc. Have we not here a suggestion as to the causation of hereditary cataracts?

(5) *Diabetic Cataract*

As a type of cataract associated with general diseases we will take that occurring in a diabetic patient.

A cataract occurring in a diabetic patient is not necessarily a diabetic cataract; thus a cataract in an elderly patient with

glycosuria may be of the ordinary senile variety. On the other hand, we sometimes find a rapidly developing change taking place in the lens in young people who are suffering from genuine diabetes; the changes are often slight and may only consist in the presence of flaws in its substance rather than genuine opacities. If these changes are associated with diabetic retinitis, the diabetic origin is increasingly probable. The cataract in young diabetic patients often develops rapidly, and is evidently a direct or indirect effect of the metabolic disorder to which the glycosuria is due. The amount of sugar in the aqueous humour is not sufficient to account for the opacities, but if we imagine a degeneration of the capsule epithelium, resulting from some product of the pathological metabolism present in diabetes, we may suspect that the capsule no longer prevents the cataract-producing poison in the aqueous humour passing through it to the lens fibres. The same line of argument may be taken in those cases associated with albuminuria and general vascular disease, as here also interference with the normal aqueous humour may follow pathological changes in the ciliary body.

(6) *Traumatic Cataract*

Under this heading we include not only gross injuries to the lens capsule and lens fibres, but also those cataracts due to ultra-violet rays, heat, cold and lightning. Lens opacities develop in fish exposed to ultra-violet rays if the tanks in which they swim are filled with water to which sodium and calcium silicate have been added. Burge [8] concludes that ultra-violet radiation kills the living cells and tissues by changing the protoplasm of the cells in such a way that certain salts can combine with the protoplasm to form an insoluble compound or coagulum.

Glass-blowers' cataract is probably due to the intense heat emitted by the furnace before which the workmen have to stand when extracting the molten glass; this heat is supposed to damage the epithelium of the lens capsule.

We may argue from a general survey of these diseases that cataract is associated with two main factors, one chemical and the other traumatic; that all the diseases associated with cataract can be referred to a condition in which a bio-chemical factor is suspected, or in which a definite traumatism occurs which damages the lens epithelium. Sometimes both these factors are associated.

(7) *Senile Cataract*

We must allow that the sub-capsular, which is the most common form of senile cataract, starts from an increased permeability to water on the part of the external cell elements of the lens. If we imagine that, owing to a diminished resistance in the epithelium of the capsule, a hydrolytic ferment is able to reach the lens fibres, we then have a ferment brought into close contact with the parenchymatous cells of the lens itself—that is, with living protoplasm. If the cell membrane can still resist, the lens fibres are saved, but I would suggest that senile cataract is due to some toxic agent, such as a hydrolytic ferment passing through the lens capsule and reaching the lens fibres themselves. In traumatic cases the injury probably allows the ferment to reach the fibres directly, but in senile cataract it is the fall of the last means of defence—the resistance of the cell membrane—which initiates the process of hydrolysis and digestion. In a soft young lens this would result in solution, but in an old one solution is prevented by the slowness of the metabolism and the inertia of the nucleus, and opacity alone results.

In conclusion let me recapitulate the main points on which I have touched. Firstly, I believe that primary senile cataract is due to a hydrolytic change in the protein constituents of the lens. Digestion of protein material is brought about by hydrolysing enzymes, which convert it into amino-acids, among which are leucin and tyrosin, which have been found in cataractous lenses. In the aqueous humour an enzyme is usually present, which is in a colloidal state and would not permeate the capsule unless gaps or pores were present. The capsule of the lens prevents the ferment reaching the lens fibres, osmosis of the aqueous humour (minus the ferment) occurs normally in order to supply the lens fibres with nourishment. As a result of traumatism or pathological degeneration of the capsule and its epithelium, the resistance is broken down and the last barrier to the ferment action—the cell membrane—is reached. If this also yields and the ferment action is powerful or the attack is prolonged, the slow and gradual process of senile cataract is started. It is suggested that senile cataract is due to a noxious chemical substance such as an enzyme reaching the lens fibres themselves.

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OBSERVATIONS ON A BOY WITH CONGENITAL DEFICIENCY OF THE ANTERIOR ABDOMINAL WALL MUSCLES

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CONGENITAL deficiency of the anterior abdominal musculature is a rare condition, which is almost always associated with some defect of the genito-urinary system. The boy, who forms the subject of this paper, was first seen in 1909 at Guy's Hospital by Mr. W. M. Mollison, who published a full description of his condition at that time in the *Guy's Hospital Reports*.[1] He was recently admitted under Dr. A. F. Hurst for symptoms of uræmia, and on his recovery was investigated as to the condition of his abdominal muscles, the position of the abdominal viscera, the acts of defæcation and micturition, his physical efficiency and the condition of vaso-motor tone.

DESCRIPTION OF CASE

Eric J., æt. 15 years, office-boy, was noticed to have a peculiar condition of his abdomen at birth. He was, however, quite healthy until he was eighteen months old, when he was treated for bronchitis. A month later he was sent to Guy's by his doctor on account of his interesting abdominal condition, and was seen by Mr. W. M. Mollison. He appeared to be healthy, and could stand and run about normally. The appearance of his abdomen was striking; the skin was wrinkled and there were two or three vertical furrows between the ensiform cartilage and the umbilicus. The latter appeared to be normal except that it was a little dragged out longitudinally. When the patient stood up the abdomen sagged, so that the lowest part partially hid the external genitals; when lying down the abdomen bulged laterally. On palpation no resistance was felt, even when he cried, except in the region of attachment of the recti to the thorax. There appeared to be almost complete absence of the anterior abdominal muscles. The quadrati lumborum were present, and no other muscular defect was found. Dr. A. F. Hurst obtained no response on testing the abdominal wall electrically.

On deeper palpation of the abdomen coils of intestine could be easily felt; the spleen could be grasped, and the liver edge was two inches below the costal margin. Neither the kidneys nor the ureters could be detected with certainty; the bladder was not palpable. The penis was well developed and the prepuce easily retracted; the scrotum was small and the testes were undescended; there was no sign of any hernia.

The thorax was small, Harrison's sulcus being well marked. The patient's bowels were regular, and micturition was normal.

When 2½ years old the child was still perfectly healthy. He was now rather more resistant to palpation in the upper part of the abdomen. "The recti appear to be present to a certain extent and are represented by two bands attached to the thorax in the normal position, these bands fading away a short distance below the umbilicus; below this the fingers can be sunk into the abdomen without meeting any resistance whatever. The lateral parts of the abdominal wall are flaccid as before. The kidneys are not palpable, nor are the ureters, nor is the bladder." [1]

At five years of age the boy remained quite healthy and without functional trouble of any kind. About this time he commenced to wear an abdominal belt.

In September 1919, when twelve years old, he was admitted under Mr. C. H. Fagge for profuse hæmaturia, drowsiness, left-sided abdominal pain and vomiting. The urine contained blood, pus and albumen. The blood urea was 0·46 parts per thousand compared with the normal of 0·3 parts per thousand.

X-ray examination showed a normal alimentary tract with a high stomach; the large gut was normal in position. The left kidney was very large, but it was doubtful if the right kidney was enlarged, as the shadow was not well seen.

Since this attack the patient has had four or five similar attacks of abdominal pain, vomiting and drowsiness.

On September 24, 1922, the patient was admitted to hospital under Dr. A. F. Hurst in a delirious condition, with pain and vomiting. His urine contained much pus, albumen and blood. He had pain in the lower part of his abdomen over the pubes and his vomitus was streaked with blood. During delirium he struggled continuously and was incontinent; his face was flushed and his eyes glassy. The blood urea was 0·6 parts per thousand.

The exact nature of these attacks is a matter for speculation. X-ray examination of the genito-urinary tract has revealed nothing abnormal. The patient is unable to empty his bladder completely, so that the abdominal pain, hæmaturia, albuminuria and pyuria can all be accounted for by recurring attacks of cystitis due to retention of urine. The delirium, vomiting and struggling appear to be due to uræmia, caused by suppression of urine following the back-pressure caused by complete retention.

The patient recovered from this attack within a week and the following observations were then made.

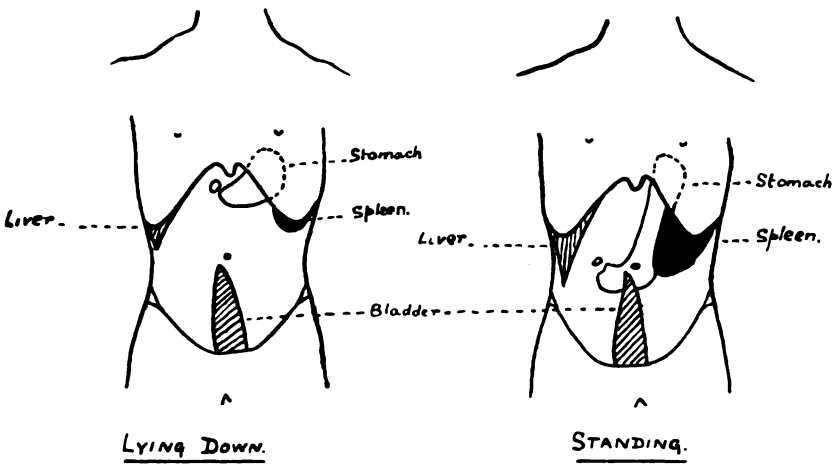
Inspection

When lying down the patient had a frog-like belly; on standing up his abdomen sagged down; the outlines of spleen, bladder and coils of intestine, with peristalsis taking place, could be seen.

The testicles were undescended and could not be palpated in the inguinal canals. The abdomen showed a number of longitudinal and transverse furrows. The patient could not rise from the supine position unless he used his arms as levers; the umbilicus was elongated vertically. Harrison's sulcus was still seen.

Palpation

The abdomen presented very little resistance anywhere on palpation, and there was no increased resistance when he raised his head. The skin appeared to be thickened; both kidneys



were palpable, and the liver and spleen could be held between the fingers and thumb, especially when the patient was standing up. The bladder could be felt as a pyriform swelling extending up to, and just to the right of the umbilicus.

The boy complained of no pain or tenderness on palpation.

Measurements.

		At end of Expiration.	At end of Inspiration.
Standing.	Girth at umbilicus.	70½ cms.	75½ cms.
	,, 7 cm. below umbilicus.	72 ,,	79½ ,,
Lying down.	,, at umbilicus.	68 ,,	72½ ,,
	,, 7 cm. below umbilicus.	70 ,,	73 ,,

Whilst lying down the spleen moves 7½ cms. vertically and the liver 3½ cms. during extremes of respiration.

Weight	= 51 kilograms.	
Trunk Height	= 83·5 cm.	
Total Height	= 164 cm.	
Chest Measurements	= 75 cm.	Expiration.
	81 cm.	Inspiration.

Faradic stimulation of all parts of the abdominal wall failed to give any response. A motor point in the eighth intercostal space on both sides was found, stimulation of which caused skin and umbilicus to be drawn upwards and outwards. The upper part of both external obliques is probably present in a rudimentary form.

Respiratory System

The rate of respiration and the ventilation showed such erratic variations due to excitement that no great value can be attached to the results obtained.

Vital capacity—2350 c.cs.

From Dreyer's tables [2] the average vital capacity for a boy of the same weight and trunk height is—

Class A : 3553 c.c.
Class B : 3244 c.c.
Class C : 3034 c.c.

The value is thus well below that of the class of least fit persons.

TABLE I.

Excursion of Diaphragm (measured on x-ray screen).

	Right.	Left.
Ordinary Breathing	1″	1″
Extremes	1⅞″	1¾″

Average normal for extremes of breathing 2½″–3″.

It is obvious that during quiet breathing the patient's diaphragm is able to function sufficiently without the aid of the abdominal muscles. The fact that the maximum excursion of the diaphragm and the vital capacity are below normal shows that the boy is at some disadvantage during deep breathing owing to the deficiency of the abdominal musculature. This is confirmed by his statement that at football he is unable to keep up with other boys.

Sir Charlton Briscoe has since investigated the patient's thorax, and can find no abnormality in the respiratory mechanism.

Cardio-Vascular System

Pulse rate.—The pulse rate was determined with the patient in various positions.

TABLE II.

Position.	Patient wearing Curtis belt.	Patient without belt.
Standing . . .	88 per min.	95 per min.
Sitting . . .	84 „ „	84 „ „
Lying . . .	80 „ „	77 „ „

These are average values and are within the normal limits according to Guy.[3]

Increase in pulse rate from lying to standing position is 8 per min. with the belt; the increase is 18 per min. without the belt. This greater increase is one of the means by which the boy maintains an adequate blood pressure on standing.

Blood pressure.—Blood pressure readings were taken with an ordinary mercury sphygmomanometer by the auscultatory method with the patient in various positions both with, and without, his belt.

TABLE III.

No.	Date.	Pressure in mm. Hg. Head lower than feet.		Pressure in mm. Hg. Lying flat.		Pressure in mm. Hg. Sitting.		Pressure in mm. Hg. Standing.	
		Without belt.	With belt.	Without belt.	With belt.	Without belt.	With belt.	Without belt.	With belt.
1	16.10.22	Sys. 113	113	—	—	—	—	—	—
		(80)	(82)	—	—	—	—	—	—
		Dias. 83	85	—	—	—	—	—	—
2	17.10.22	Sys. —	—	108	107	93	91	102	104
				(84)	(88)	(83)	(82)	(96)	(88)
		Dias. —	—	77	80	67	73	78	79
3	17.10.22	Sys. —	—	110	110	100	103	112	114
				(64)	(71)	(85)	(86)	(94)	(88)
		Dias. —	—	85	90	75	83	78	80
Average.		Sys. 113	113	109	108·5	96·5	100	107	109
		(80)	(82)	(74)	(80)	(84)	(84)	(95)	(88)
		Dias. 83	85	81	85	71	78	78	79·5

The figures in brackets indicate the pulse rate taken at the time of the blood pressure reading.

Series No. 2 was done in the following order :—

Lying flat with belt, lying flat without belt, sitting without belt, sitting with belt, standing with belt, and standing without belt.

Series No. 3 was done in the following order :—

Standing with belt, standing without belt, sitting with belt, sitting without belt, lying flat with belt, lying flat without belt.

The results show :—

(i) A fall in blood pressure, both systolic and diastolic, when the patient assumes the sitting position from the recumbent position, and a rise again when he is standing. This occurs in the patient both with his belt on and off.

(ii) In any position the wearing of a belt alters the systolic pressure very little indeed, the change being in the form of a slight increase. There is also a small, but somewhat larger, increase in the diastolic pressure.

(iii) On standing the boy compensates well as regards pulse pressure.

The patient has on several occasions not worn his belt for a period lasting three or four hours, and, although walking about during that time, he has not felt any signs of faintness. The question that may be raised is, " Why does his blood not stagnate in the abdominal vessels and so cause cerebral anæmia ? "

In the normal individual the return of blood to the heart from the abdomen is largely determined by (i) the tone of the abdominal muscles, (ii) the tone of splanchnic vessels, (iii) the pumping action of the respiratory movements.[4]

In this boy the first factor does not come into play, and we have also seen that in quiet breathing his respiratory movements are within the normal range. It appears then that his splanchnic vessels must be in a hypertonic condition.

It was thought that perhaps an indication of increased tone in the splanchnic vessels would be shown by an increased tone in the vessels of the lower extremities. Simultaneous blood pressure readings were taken from the brachial and posterior tibial arteries, both in the recumbent and standing positions.

TABLE IV.

Position.	Brachial pressure in mm. Hg.	Post. tibial pressure in mm. Hg.
Recumbent . . .	113	128
Standing . . .	110	168
Recumbent . . .	113	126

Difference between pressure in brachial artery and posterior tibial artery when standing = 58 mm. Hg. Difference in height between the two armlets = 70 cm. approx = 54 mm. Hg. approx.

Thus the increase in pressure in the posterior tibial artery on standing is just sufficient to counteract the effect of gravity as in an ordinary individual,[5] and gives no indication whatever of the tone of the splanchnic vessels.

Surface temperature as an indication of peripheral vascular tone.—The surface temperature at various parts of the body are recorded in the following table :—

TABLE V.

WITH BELT ON.

	Right.	Left.	Mean.
Hand . . .	34·5° C.	35·5° C.	35° C.
Arm . . .	30·4	31·6	31
Leg . . .	30	30·6	30·3
Cheek . . .	30	28·6	29·3

WITH BELT OFF.

	Right.	Left.	Mean.
Hand . . .	35·6° C.	36·3° C.	35·9° C.
Arm . . .	31·2	30·6	30·9
Leg . . .	30·1	30·3	30·2
Cheek . . .	29·8	28·6	29·2

Temperature of room { Wet bulb 10·4° C. / Dry bulb 14° C.

On comparing the above results with those obtained on normal individuals by Pembrey and Shipway,[6] it is seen that the boy maintains his surface temperature within the normal limits, and shows again how well his bodily reactions are compensated.

PHYSICAL EFFICIENCY

(*a*) *Flack's 40 mm. test.*[7]—The patient, seated, held up the mercury in a U-tube manometer to a height of 40 mm.

The pulse in the radial artery at the wrist was noted before, during and immediately after the test. An interval of three to five minutes was allowed between each test.

TABLE VI.

WITHOUT BELT.

Time of test.	Pulse Rate.			Remarks.
	Before test.	During test.	Immediately after test.	
16 secs.	96 per min.	Pulse not felt.	69 per min.	No extra-systoles.
21 ,,	98 ,, ,,	,, ,,	69 ,, ,,	? 2 extra-systoles after test.
15 ,,	85 ,, ,,	,, ,,	71 ,, ,,	? 2 extra-systoles after test.

The volume of the pulse was always much greater in the after period.

TABLE VII.

WITH BELT.

Time of test.	Pulse Rate.			Remarks.
	Before test.	During test.	Immediately after test.	
24 secs.	96 per min.	First 6 beats felt. Last 22 ,, ,,	75 per min.	? 2 extra-systoles after test.
31 ,,	96 ,, ,,	First 9 beats felt. Last 33 ,, ,,	74 ,, ,,	No extra-systoles.
30 ,,	93 ,, ,,	First 6 beats felt. Last 42 ,, ,,	70 ,, ,,	No extra-systoles.

The volume of the pulse was always much greater in the after-period.

The pulse could not be felt during the test except those beats stated in the above table. The boy with his belt was able to hold up the mercury for a longer time than without it, and some of the beats could be felt during the test, whereas none could be distinguished when the boy was not wearing the belt.

Graphic records were also taken of the pulse rate before, during, and 40 secs. after holding up the mercury in the U-tube manometer. The response of the pulse rate and of the systolic blood pressure when an abdominal bandage was worn was found to give results very similar to those of the average fit subject. When the bandage was not worn, the average pulse rate during the holding period was at a higher level (by about 10 beats per minute) than when the belt was worn. This was due partly to the pulse rate attaining an initial higher level, and partly to an almost complete absence of recovery towards the normal, for a certain amount of recovery does take place if the support is worn. The pulse rate after the test showed the usual

subnormal phase, which was not more marked when the abdominal belt was missing.

These results confirm the work of Warner and Hambly [8] which shows that when there is a good abdominal tone the pulse rate during the test does not rise to the same extent, and recovers more readily than when the tone is poor.

(*b*) "*Pulse ratio*" *test.*—The pulse rate was taken during rest and during the two minutes immediately following walking up and down 24 test steps (each 13" high) per minute for a period of three minutes. Observations were made on the boy both with his belt on and with it off.

Belt on.—Pulse ratio =

$$\frac{\text{No. of beats during two minutes after exercise}}{\text{No. of beats at rest for one minute}} = 2{\cdot}46.$$

This according to Hambly, Hunt, Parker, Pembrey and Warner [9] is a very good average.

Belt off.—Pulse ratio = 2·56.

In this case the boy was not quite so fit.

Digestive System

X-ray examination.—The stomach was found to have normal tone and to be if anything, rather high. It did not move more than normally on changing from lying to standing position. (The boy was not wearing his abdominal belt when examined.) This is evidence in favour of the view that the normal position of the stomach is maintained less by the intra-abdominal pressure produced by the abdominal muscles than by the tone of the gastric musculature.

Defæcation.—The bowels are open regularly and without difficulty every day, usually once, but sometimes twice. X-ray examination showed that during a pretended act of defæcation the diaphragm descended to the position of deepest inspiration. The patient does not bring into play any unusual accessory movements, such as pressure on the abdomen with his hands.

Hurst [10] points out that in the baby the act is reflex; in the normal adult the act is initiated voluntarily, and later largely carried out voluntarily by the abdominal muscles. In this boy the initiation is voluntary, and the act is partly voluntary by the assistance of the diaphragm, but it is still largely reflex.

The tension of the skin and connective tissue prevents the abdominal wall from bulging sufficiently far to annihilate the increase of intra-abdominal pressure, produced by the descent of the diaphragm.

Micturition

Patient was seen during the act of micturition. The stream of urine was rather weak, but on encouragement he could make the stream much stronger. The patient said he usually did not make a strong stream. Here, again, no unusual accessory movements were brought into play.

Other Cases

Garrod and Davies [11] in 1905 described two cases and gave the literature of eight others. Since then Bolton,[12] Hall,[13] and Thatcher,[14] who also gives the literature, have described other cases. In all but three the bladder has been described as occupying the fœtal position. Most of these cases also showed enlargement of one or other kidney with dilatation of the ureters.

Summary and Conclusions

The general conclusion is that, in spite of the deficiency of anterior abdominal wall musculature, the boy shows remarkably little functional disability.

Never having experienced that sense of support usually afforded by the anterior abdominal muscles, he feels no ill effects due to dropping of viscera, although the liver and spleen are very low and the small intestine bulges forward.

The fact that the stomach is orthotonic necessitates some other explanation as to its support; its inherent tone and attachment of its extremities are important factors.

Defæcation is assisted by voluntary movements less than normally, and is therefore largely a reflex act. The initiation of the act is, however, voluntary and due to contraction of the diaphragm.

The bladder is not emptied with the normal facility owing to the absence of the reinforcing action of the anterior abdominal muscles. The consequent cystitis and its results show that this is his greatest disability.

Circulatory compensation is nearly perfect. Increased tone of the splanchnic vessels compensates for the absence of tone in the anterior abdominal wall in assisting the return of blood to the heart from abdominal vessels. Symptoms of cerebral anæmia are in this way prevented.

The respiratory mechanism does not differ in any material respect from normal. The vital capacity is, however, definitely below normal, and this is one factor in rendering the patient unable to take severe muscular exercise.

Flack's 40 mm. test shows that when wearing a belt his physical efficiency is about the same as that of an average person, but without the belt he is to be classed in a lower grade. These results are confirmed by the " pulse ratio " test.

In conclusion we should like to thank Dr. A. F. Hurst for permission to publish the case and for his help, and also Professor M. S. Pembrey, Dr. J. M. H. Campbell, Dr. J. J. Conybeare, and Sir Charlton Briscoe for their help and interest.

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CASE OF CONGENITAL DEFICIENCY OF ABDOMINAL MUSCULATURE

WITH POST-MORTEM REPORT

By N. L. ECKHOFF.
(From the Department for Diseases of Children, Guy's Hospital.)

P. P., a male baby, the first born, was brought up to Out Patients at the age of ten days, owing to alarm about the size of his abdomen. The only symptom up till this time was the presence of a streak of blood on two or three occasions in the urine on the third day.

He was admitted to the Children's Ward under Dr. H. C. Cameron for further investigation, the case being recognised as one of deficiency of the abdominal musculature.

He was taken home by his anxious mother after a few days, but was readmitted some weeks later, much thinner and more wasted, with otorrhœa and pyrexia. The ear discharge ceased on treatment, but an intermittent pyrexia continued.

The abdomen was obviously enlarged, bulging in all directions, more particularly into the right flank. When the child was raised the abdomen hung over the pubes like a large ventral hernia.

The skin of the abdominal wall was wrinkled and furrowed. The umbilicus was a mere transverse slit, no cicatrix being visible. The skin lacked elasticity and appeared stretched, though not actually thinned.

Peristalsis was visible, and coils of gut could be made out.

The whole abdomen had a doughy consistence on palpation. Some slight resistance was encountered between the costal margin and the umbilicus on each side. The hand could be pressed deeply inwards from the front and at the sides. Behind, there was definite resistance in the position of the quadratus lumborum, and the erector spinæ appeared to be intact.

The large size of the bladder immediately attracted notice. It extended up as far as the umbilicus, with its apex at this point. It was pyriform in shape and occupied the whole of the lower abdomen.

Both kidneys were palpable, the left being definitely larger

than the right, and extending lower down. The spleen and liver were not identified. The bowel could be outlined.

The testicles were undescended, and were not in the inguinal canals. The scrotum was fully developed.

The chest was flattened from side to side, and presented an ingrooving at the site of attachment of the diaphragm. When the child hiccoughed, although the chest was forcibly drawn in by the contraction of the diaphragm, there was no sign of active movement in the abdominal wall.

The intercostal spaces were filled in and all the ribs were present.

Except for general deficiency of subcutaneous tissue, and poor development of all the muscles, no other abnormalities were found.

The child did not progress favourably, and died at the age of nine weeks after a period of increasing diarrhœa with green, acid stools.

Post-mortem Examination

The limb muscles appeared normal, though of small size. The sternomastoid and pectoralis major were present. The intercostal muscles appeared well developed, though, curiously, the triangularis sterni was absent.

Dissection of the abdominal muscles revealed the following characteristics.

The *quadratus lumborum* and *psoas magnus* were well developed on both sides.

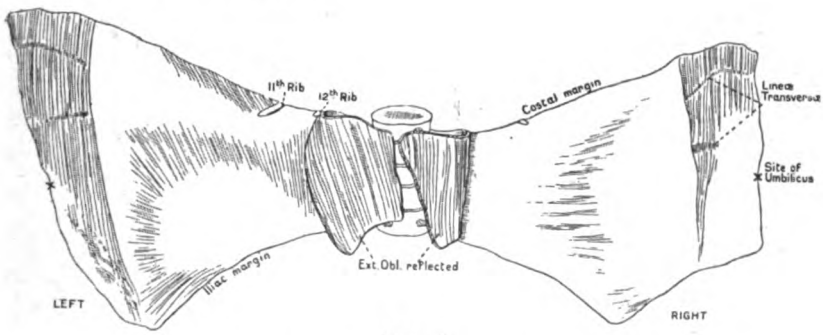

Fig. 1.

Dorsal and External view showing Internal Oblique and Rectus.

The *rectus abdominis* was present on both sides above the umbilicus, and two lineæ transversæ were seen. Below the umbilicus the muscle was deficient in its medial parts, and tailed off to a tiny strip along the lateral border (Fig. 1).

The *external oblique* was represented by a sheet of vertical

fibres, about two inches wide, between the ilium and the last rib behind.

The *internal oblique* on the right side could barely be defined. On the left a narrow strip about half an inch wide ran along the costal margin, and a similar strip ran forwards in the middle of

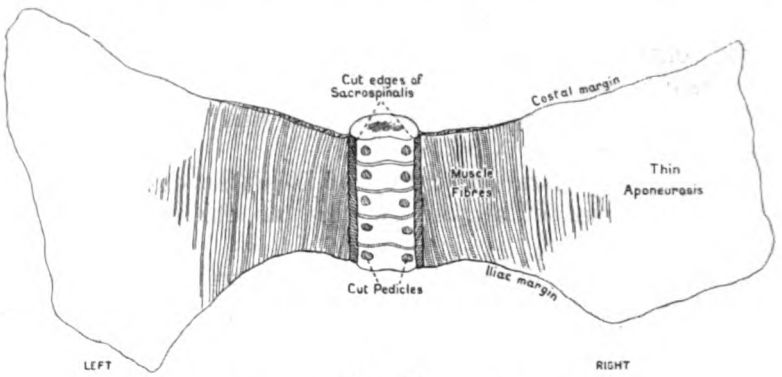

FIG. 2.
Dorsal and External showing External oblique only.

the sheet, turning downwards along the lateral margin of the rectus (Fig. 2).

The *transversalis abdominis* existed only as a thin strip along the costal margin, and a few fibres near the anterior superior

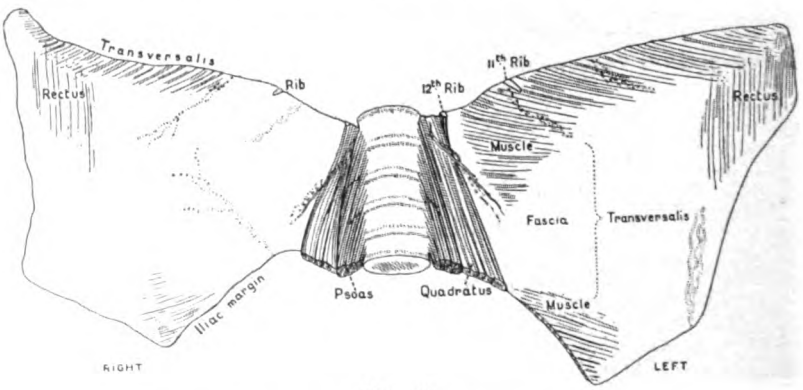

FIG. 3.
Internal (Abdominal) view showing Transversalis and Rectus.

iliac spine. On the right there were fewer fibres than on the left (Fig. 3).

In spite of this great deficiency of muscular tissue, the existing fibres appeared normal on microscopical examination, and the nerves and vessels were demonstrated both by the naked eye and microscopically.

It will be noticed that the deficiency was most marked below and in front—that is, in the area in relation to the bladder. The viscera presented many unusual features.

In the first place the bladder occupied a large part of the abdomen, extending upwards for 2½ inches.

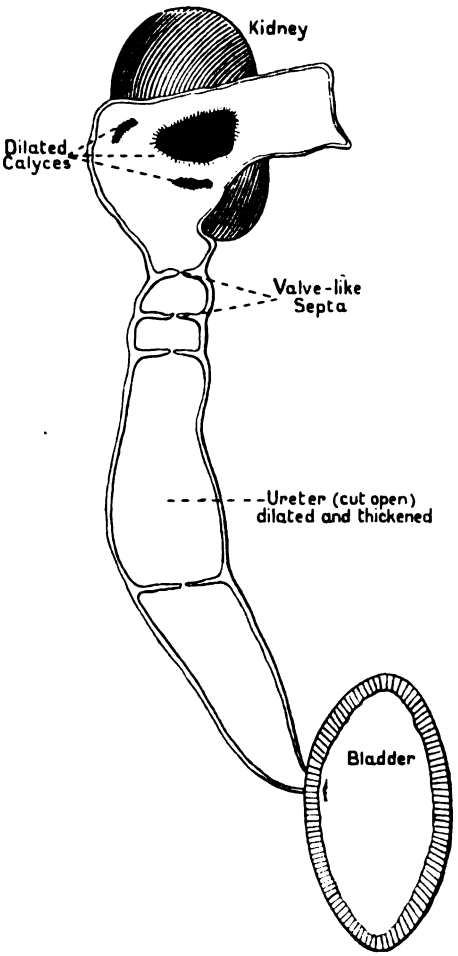

FIG. 4.
Left kidney, Ureter (unravelled) and Bladder.

A segment of colon lay transversely, immediately above this, and small gut was visible at the sides.

The liver was displaced to the right, and the ligamentum teres therefore ran very obliquely. The liver was so bent upon itself along a vertical axis, that the left lobe lay in front of the right lobe, and both were to the right of the mid-line.

The right hypochondrium was occupied by the stomach,

and the cæcum and appendix were discovered immediately below this organ. The transverse segment of colon noticed when the abdomen was first opened proved to be the ascending colon, and the true transverse colon lay doubled up behind this, terminating in the usual way.

The bladder was enormously dilated and hypertrophied. It measured nearly 3½ inches in length and was about ⅓ inch thick. The mucous membrane was smooth and not rugose, and appeared quite healthy.

The ureters were also enormously dilated and hypertrophied, and looked like coils of small intestine as they lay undisturbed. When cut into and unravelled they were found to be of enormous length, the left being nearly 12 inches long. The walls were pocketed and sacculated with valve-like interruptions, somewhat resembling the valvulæ conniventes of the small bowel.

The pelves of the kidneys were dilated and opened into dilated calyces. The left kidney was much larger than the right.

The genital organs appeared normal. Muscle fibres in the peritoneum near the testis suggested the presence of a gubernaculum, although the testicles lay loose in the pelvis.

Summary

Examination thus revealed a marked deficiency of muscles forming the anterior and lateral parts of the abdominal wall, although the blood and nervous supply to these regions appeared unimpaired.

It also demonstrated extreme dilatation and hypertrophy of the bladder, ureters and pelves of the kidney, and some malposition of other abdominal viscera.

The theory put forward by Stumme [1] seems to explain the possible causation of the condition. Although no obstruction to urinary outflow was apparent during life, and no urethral obstruction was demonstrated post-mortem, it seems conceivable that enormous intra-uterine dilatation of the bladder could have caused pressure atrophy, or a failure of the abdominal muscles in immediate contact with it to develop, and possibly too a failure of the cæcum to descend.

The nature of the obstruction that would produce this dilatation of the urinary organs in intra-uterine life, and not be apparent after birth, must at present remain a matter of conjecture.

I am indebted to Dr. H. C. Cameron for permission to publish this case.

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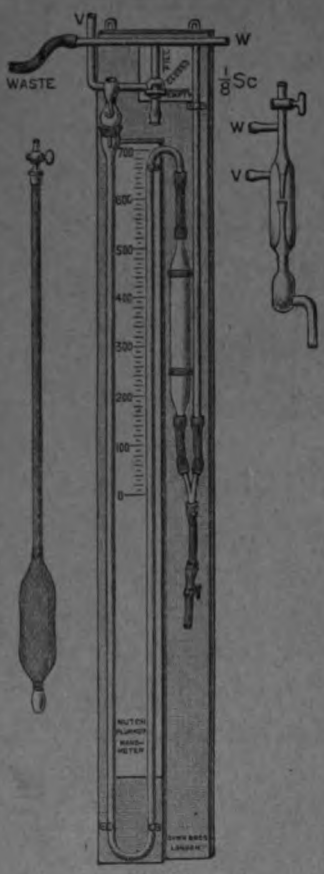
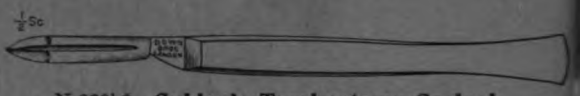
INDEX

RECENT INSTRUMENT

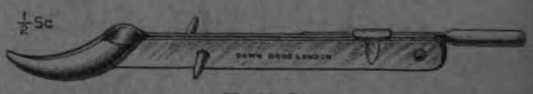


N 570
Nathan Mutch's Cardio-Spasm Apparatus.

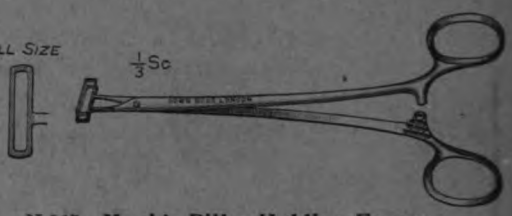


N 220b* **Cubley's Tracheotomy Scalpel.**

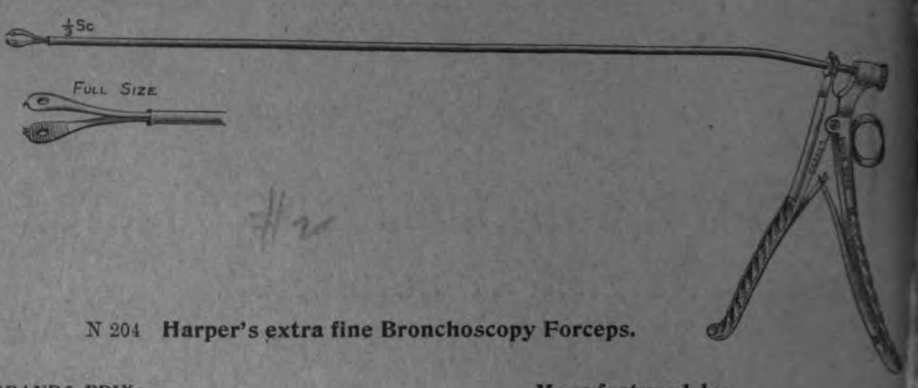
N 217a* **Cubley's Tracheotomy Artery Forceps.**



N 220a*
Cubley's Dilating and Introducing Forceps.



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



N 204 **Harper's extra fine Bronchoscopy Forceps.**

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Paris, 1900. Brussels, 1910.
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TI1