ance. From this day no departure from the normal mental state could be detected; walking in the garden and downstairs at meals as usual; easily tired.

Note.—The alternate good and bad nights refer to sleep only, the alternation being a marked feature in several of the previous cases dealt with. A loss of one night's rest during the period of recovery need be looked on without anxiety.

CASE IX.

On August 18th, 1899, I saw, in consultation with Dr. Reid, Shanghai, a married woman, aged 30, who had been nursing an 8 months' old child till the 13th. She was suffering from acute delirious mania, which had then lasted seven days, was refusing food and being fed by the bowel, under forcible restraint to prevent injury to herself, had had only one night's sleep in six, and was occupied incessantly in noisily talking, singing, and on the move as far as the restraint allowed. By my advice, on the 18th 7 drachms of sodium bromide were given in three doses before 7 P.M. by a catheter through the nose. That day she had had 30 gr. chloral hydrate and 1 drachm bromide.

Second Day.—She slept the greater part of the night, but still refused food, was restless and talkative all day; 7 drachms of bromide were given before 4 P.M. by the nose.

Third Day.—She slept all night; talked quietly through the day, no longer needing restraint; took some milk by the mouth and ate a little bread; 7½ drachms bromide were given before 4 P.M.

Fourth Day.—Slept all night, and could not be roused to wakefulness; she puts out the tongue on being asked to do so, and is muttering indistinctly; before 9 A.M. she had drunk 16 ounces of milk readily; at 3 P.M. temperature 105°, pulse 100. The left parotid region was much swollen and the left breast when touched caused her to wince; a set of false teeth were removed from the mouth, which was found in such a state as to evidently account for the swelling on the left side of the head; the mouth was ordered to be regularly cleansed with boric acid solution.

Fifth Day.—She cannot be roused, and takes no notice of the order to put out her tongue. Temperature 104° to 105° all day, except when sponged. Evident cellulitis of the left carotid, submaxillary, and neighbouring regions. She takes abundance of milk.

Sixth Day.—Still asleep; 7 A.M., temperature 105°, pulse good. Swelling somewhat less; the mouth looks cleaner. No disturbance of respiration or cough; no physical signs of abnormal character in the chest. Temperature at 4 P.M. 108°. Died at 8 P.M.

No post-mortem examination was made. Death was obviously due to septic poisoning starting in the condition of the mouth, overlooked from the fact that she had had no food by mouth for over a week, and that the false teeth had been previously removed, but replaced by patient about the time the bromide treatment commenced.

In this case within eight hours of the commencement of administration of the bromide sound sleep was procured; in thirty-six hours the incessant excitement of emotional, mental, and motor nerve centres was quieted, and restraint no longer needed; in sixty hours complete rest of these centres was established, and food was no longer refused. Had the septic mischief not supervened, these results should have tended towards recovery of a condition difficult to deal with in private, and serious in proportion to the duration of the exhausting manifestations.

By removal to an asylum, thus cutting off impressions from the surroundings to which a patient is accustomed, and in which an acute mania may have arisen, it is hoped that the receptive side of the nervous system will be rested to some extent. It is also hoped by this cutting off of accustomed stimuli that some rest will be secured for the regulative and executive side of that system, in which in all probability the greatest part of the disturbance is taking place, and more especially in its relation not to direct impressions, but to registered ones—memory. The only means of procuring complete rest for these higher parts of the nervous system, as well as for lower centres, is through sleep, natural and artificial. It will be conceded almost on every hand that the production of artificial sleep hitherto by hypnotics leaves much to be desired in the presence of states like acute mania. In the bromide sleep there is the certainty of rest to both receptive and executive sides of the nervous system, and also of the region concerned with memory, a rest so complete and prolonged as can be obtained by no other means as safely. If future experience goes to show, as I venture to hope it will do, that this bromide sleep can be induced without or with little danger, it ought to prove a powerful and effective means of dealing with all maladies of the nervous system in the treatment of which there is need for deep sleep, and a profound and prolonged rest of the higher centres.

REFERENCES.

- ¹ BRITISH MEDICAL JOURNAL, July 10th, 1897, p. 76; and April 15th, 1899, p. 896. ² *Ibid.*, p. 897.

A CASE IN WHICH 300 GRAINS OF SULPHONAL WERE TAKEN IN TWO DOSES.

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In the BRITISH MEDICAL JOURNAL for November 4th, 1899, in a paper by Dr. A. H. Bampton, on The Toxic Cumulative

Effect of Sulphonal and Trional, the following passage occurs: "It is lamentable that such powerful drugs as sulphonal and antipyrin in bottlesful are allowed to be sold to the public for secret self-drugging purposes." The matter was also referred to in an editorial article in the JOURNAL of December 9th. The following case, which recently came under my notice, is of importance with reference to the question of the easy way in which patients can obtain large doses of drugs which, though harmless in small doses, and under proper supervision, yet are toxic if taken in sufficient quantities.

On April 27th, 1899, I was asked to see and if necessary sign a medical certificate of unsoundness of mind in the case of a lady suffering from melancholia. Depression had been intermittently present since the birth of her third child some two years before, and she had already been under care in two asylums, with only partial improvement. Two days before I saw her she had taken 150 grains of sulphonal, which she had obtained from a chemist's in the form of six powders of 25 grains each. Her husband, a medical man, on learning this, gave her apomorphine hypodermically, and a purgative by the mouth, and these drugs acting efficiently, no toxic effects of the sulphonal followed. She had, however, another 150 grains, which she had obtained in the same way, and had secreted in her stocking, and this she took the day before I saw her. Resort was again had to emetics and purgatives, and nothing but drowsiness resulted from the large dose. She was very depressed; thought her soul was lost, and that God told her so, and had visions of the "dead and dying." She said she had taken the two enormous doses of sulphonal for "no reason." She acknowledged that she did not want to live, but said she had merely taken the sulphonal to produce sleep. Her husband told me that she had often taken poisonous doses of drugs, and on one occasion took lin. chloroformi. At one time also she suffered from hæmorrhage from taking sulphonal. There was no difficulty in certifying her as insane.

On inquiry at the chemist's where she said she had obtained the drug as to whether it was possible for a patient to obtain such a quantity without a prescription, I was assured that there was no difficulty about the matter, and that no suspicion would be excited by a patient asking for six powders of 25 gr. each. Moreover there is no difficulty in buying bottles containing tabloids of 5 gr. each, which would easily mount up to any dose a patient might think fit to take. Fortunately in this case no evil results followed, but it is quite conceivable that the case might have ended very differently, and although the toxic effects of sulphonal are usually produced slowly, and as the result of taking the drug in ordinary doses for a long time, yet it would appear that there ought to be some restriction on the possibility of patients purchasing large amounts.

It is worthy of note that in this case the drug was not obtained in the form of a proprietary article, but in the form of a standard B.P. preparation without a prescription.

A CRITICISM OF THE MECHANICAL HYPOTHESIS OF THE ORIGIN OF CARCINOMA,

WITH A DESCRIPTION OF A SPECIMEN OF "SPONTANEOUS" CARCINOMA OF THE UTERUS IN THE RABBIT.*

By SAMUEL G. SHATTOCK, F.R.C.S.,

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THE specimen which I exhibit is a highly-marked one of carcinoma in the rabbit, and was from an animal upon which no kind of experiment had been performed. Both uteri are the seats of multiple and extensive tumours. Histologically the growths are of the columnar-celled kind, in places papilliferous.

Between the growths the mucosa is nearly everywhere raised in complex papillary processes, and from such areas the growth of the carcinoma can readily be traced. The mode of formation exactly resembles that of the columnar-celled carcinomata of the rectum, many of which are also papilliferous. There were a certain number of disseminated peritoneal growths.

The interest of this specimen relates almost exclusively to the bearing it has upon the experiment put on record by Dr. Lambert Lack in the *Transactions of the Jenner Institute*, vol. ii, and the *Journal of Pathology*, August, 1899.

The experiment was carried out by laying open the ovaries of a rabbit, scraping the surfaces, and allowing the milky juice containing free epithelial cells to diffuse into the peritoneal cavity, the laparotomy wound being, of course, afterwards closed. The particular animal remained well for nearly

* Read at the meeting of the Pathological Society of London, January 16th.

a year; it then became thin and weak, and commenced to suffer from dyspnoea; two months later it was killed. The abdominal cavity was studded with carcinomatous foci, and there were other foci in the thorax. The condition of the ovaries is not stated. The uterus was greatly thickened; its mucosa papilliform, and at one place in its wall was a tumour as large as a cherry.

This is the experiment, and the hypothesis is that the displacement of normal epithelium into a lymph space or lymph cavity is sufficient to bring about the growth of a carcinoma.

The most ominous feature in the *post mortem* finding is the condition of the uterus, for the state of the uterine mucosa is precisely like that in the specimen exhibited, in which it is easy to trace the source of the carcinoma of the uterine wall from the morbid mucous membrane; the size again of the uterine tumour exceeds that of the peritoneal growths, nor is a sufficient histological account of the uterine changes furnished to judge whether the tumour noticed was the only carcinomatous formation present in the uterus, or one of others that may have escaped notice because less prominent. The author, it is true, speaks of the structure of the various tumours as corresponding with that of "ovarian carcinoma," as though there were something unique and diagnostic in the latter; but this cannot be allowed, for similar carcinomata are met with not only in the thyroid, breast, rectum, kidney, etc., but, what is most to the point, in the uterus of the rabbit itself.

In coming to his conclusion as to the causal relationship between his experiment and the disease found after death, Dr. Lack was influenced largely by the statement of Professor J. McFadyean that he (Professor McFadyean) had never seen or heard of carcinoma in the rabbit. The specimen exhibited not only shows that carcinoma occurs in the rabbit, but the uterine changes and the structure of the carcinomata are so alike in the two cases that a repetition of Dr. Lack's experiment is rendered imperative. And, unless this striking result can be repeated, it must be passed by as a coincidence, remarkable enough, but not without parallel, as the historical error of Hunter on the identity of gonorrhoea and syphilis suffices to show.

One is tempted to reverse Morgagni's aphorism, *Non numeranda sed pendenda sunt observationes*. Everything depends in this case upon the number of observations, or, rather, their number constitutes their weight.

Were the rabbit in Dr. Lack's experiment the subject of primary uterine carcinoma, no essential relationship would, of course, exist between the scraping of the ovary and the appearance of the peritoneal growths. There is, however, another possible source of fallacy in a repetition of the experiment as planned by the author. Such an injury as that inflicted upon the ovary might be followed by a carcinoma of the ovary itself, not from the dislocation of normal epithelium into the ovarian tissue, but as the sequence of an infective process set up at the injured spot, and due either to the direct implantation of a contagium vivum or to an indirect transference to it.

This possible source of error may be eliminated by adopting the method of intraperitoneal injection, and I have recently carried out such a modification of Dr. Lack's experiment upon a series of rabbits. As the results of these experiments, whether negative or positive, will be recorded on a future occasion, their details need not be now given, except to state that scrapings of the ovaries of freshly killed rabbits were suspended in warm sterilised salt solution and injected intraperitoneally into a second set of animals.

In another series a similar suspension of testicle scrapings was injected; and in a third series a suspension of ovary and testicle scrapings combined. As a yet further modification, injections of such suspensions were made subcutaneously.

What collateral evidence is forthcoming in support of what may be designated the mechanical hypothesis of the origin of carcinoma, namely, that the mere traumatic dislocation of epithelium into a lymph space is itself sufficient to bring about the growth of a carcinoma? The well-known dissemination of peritoneal papillomata which takes place after the intraperitoneal rupture or spontaneous opening of a papilliferous ovarian cyst does not really belong to this class of phenomena, seeing that such a cyst is distinctly a pathological

new formation, and normal characters cannot be safely ascribed to the epithelium investing the growths within it. Similar papillomata are at times met with arising from the surface of one or both ovaries, apart from the perforation of papilliferous cysts; and doubtless their histological characters are in this case to be explained by their origin in connection with the columnar-celled germ epithelium which normally invests the ovary, and which, indeed, originally furnishes by its ingrowth the lining of the ovarian cysts in which similar papillary formations may arise.

Such papillomata have the general features of contagious warts, and are comparable to those which arise in other positions. Setting aside the popular view as to the contagiousness of cutaneous warts, for which there is some experimental evidence, the most interesting and striking proof of this contagiousness is furnished by the papillomata occurring in the mouths of dogs. Not only is the contagiousness of such shown by the wide spread of the disease amongst dogs kennelled together (J. Penberthy, F.R.C.V.S.), but Professor J. McFadyean and Mr. F. Hobday have proved the inoculability of these growths by experiments which have sufficient general interest to justify their citation.

A series of four experiments were made. One such wart was excised from the buccal mucosa of the mouth of a young fox hound, and its cut surface was used to rub a small area of lightly scarified mucous membrane on the right upper lip of each of three dogs, namely, a pug and two fox-terriers. About a month afterwards a slight ridge of growth appeared at the site of inoculation. After attaining in the fox-terrier a size and appearance almost identical with the natural warts in the mouth of the fox-hound, they began to shrink, and eventually almost entirely disappeared. The pug was killed with chloroform, and one of the experimental warts was cut off and rubbed against a small area of scarified mucosa on the left side of the upper lip of each of the fox-terriers of the preceding experiment, and on both sides of the upper lip of a bull-terrier. The attempts to reinfest the mouths of the two fox-terriers were entirely negative in results, but on each side of the lip of the bull-terrier papillomata formed at the scarified spot.

The spontaneous disappearance of cutaneous warts in the human subject is well known, and equally so amongst obstetricians is the retrogression of the disseminated papillomata of the peritoneum which follows removal of the ovaries bearing the primary growth. This latter phenomenon is one that has excited much surprise (a striking instance is cited by Dr. Cullingworth in the *Obstetrical Transactions*, vol. xxxiv, p. 154), but, like the spontaneous disappearance of external warts, it is possibly due to the acquisition of immunity. The tumours, that is to say, may lead to their own disappearance in consequence of the elaboration of some substance antidotal to the action of another produced within the growth, and without which the growth itself would not take place, the auto-immunisation being too feeble to effect a spontaneous disappearance of the whole, but enough to bring about that of the disseminated growths after the voluminous parent masses have been removed.

Whether certain of the cases of spontaneously disappearing sarcoma in man may not come within the same class of phenomena is a speculation not unworthy of consideration. The foregoing papillomata are instances of neoplasms arising from the transplantation of abnormal epithelium. But to turn to the case of normal epithelium. The most recent work in this direction is that of Lubarsch and his pupils, Krückman and Lengemann.¹ Emulsions of various glandular organs were injected into the jugular vein of rabbits. No growth ensued in any part of the body as a result.

The list of organs used, though it comprises testicle, does not include ovary, a notable omission which needs making good. In another series of experiments small portions of glandular organs were mechanically detached and allowed to remain *in situ*, or implanted into the organs of other animals of the same kind. The fragments, even in cases where a small degree of growth ensued, before long shrank and disappeared. The history of tissue fragments detached and displaced within a glandular organ by injury in the human subject must be assumed after these experiments to be similar in kind.

In the case of the injection experiments the vascular and not the lymphatic system, it is true, was chosen.

Yet that this does not weaken the argument appears in the metastasis which regularly occurs by way of the blood stream in the course of sarcoma, and is not unknown, too, in carcinoma, as exhibited in the secondary hepatic growths that may arise in connection with columnar-celled carcinoma of the intestinal canal or rectum, or in Sir James Paget's classical case of "malignant chondroma" of the testicle, which, as proved by the late Professor Kanthack and Mr. S. Pigg, was really a chondro-carcinoma infecting the lungs by way of the spermatic veins. It follows as a corollary that, in order for an embolus to proceed to the growth of a tumour, some morbid character must be impressed upon the epithelium so transplanted.

But apart from such metastasis in malignant disease, the epidermal cysts of the palm and palmar aspects of the fingers furnish an instructive object-lesson of the results that follow the traumatic dislocation of epidermal cells into or beneath the corium, and one to which I referred on the occasion of Dr. Lack's bringing his experiment before the notice of the Medical Research Club in July of last year. I have had opportunities of examining three or four such cysts, and quite recently one which was removed by Mr. E. C. Stabb from the palm of a woman, aged 50, who three years previously had run a pin into the palm; the wound bled, and a week or two afterwards a small swelling appeared which slowly increased in size.

The cyst, as now studied, lies altogether beneath, and separated by the fibrous tissue of the corium from, the general epidermis. Its lining has, as in other examples, all the characters of true epidermis, presenting most inwardly a thick laminated layer of horn, beneath this a well-pronounced stratum granulosum, and still more deeply a rete Malpighii with a vertical set of cells set upon the fibrous tissue, which cells, though parallel, are somewhat displaced from the vertical as a result of the oblique incidence of pressure. The rete of the cyst has about the thickness of the general rete where this lies on the summits of the papillæ. The cyst has an ill-defined wall of fibrous tissue, not differentiated in its more superficial or uppermost part from that of the corium, and it is completely devoid of papillæ or glandular structures. Such cysts remain of small dimensions, the implanted tissue behaving in its after-growth much as in the experiments already cited.

After a certain amount of proliferation, growth ceases, but though epithelial cells are here displaced into the lymph spaces of connective tissue, no formation of a carcinoma ensues.

Amongst the same class of phenomena must be ranged the multiple formation of cysts which may follow the rupture of an ovarian dermoid. Here, again, there ensues a production of simple circumscribed cysts, and not a carcinomatous infection of the peritoneum such as should arise were the mechanical hypothesis of the origin of carcinoma a true one.

REFERENCE.

- ¹ *Geschwülsten und Infectionskrankheiten*, and in the *Verhandlung der Deutschen pathologischen Gesellschaft*, 1899, p. 97.

SPASMODIC CLOSURE OF THE LARYNX DURING THE ADMINISTRATION OF ETHER,

PRECEDED BY NITROUS OXIDE: MITRAL STENOSIS: ALTERNATION
OF MURMURS.

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It is known that some patients with compensated mitral stenosis are unable to take ether as an anæsthetic; the following is a case in point:

On February 6th, 1899, an undersized and very nervous youth, aged 16, a patient under Mr. Gilbert Barling, at the General Hospital, Birmingham, was brought into the anæsthetic room to be anæsthetised for the removal of the vermiform appendix. He was markedly cyanosed, especially about the nose and inner parts of the cheeks, and the finger ends were clubbed, but there was no œdema or ascites. There was no history of recent cough nor any evidence of disease found in his lungs. The heart's apex beat was diffuse, and accompanied with a marked rough thrill. A loud presystolic murmur was heard, leading up to a greatly-accentuated first

sound. The second sound was reduplicated, and there was a soft diastolic murmur preceding the presystolic, and separated from it by a short interval. The pulse was of small volume, and rapid but regular.

I gave the patient gas and ether by Hewitt's apparatus and method, using about three-quarters of a bagful of the former. After turning on the ether, I allowed a breath of air at three or four separate intervals to obviate any additional heart strain. There was no excitement or struggling, only just a little movement of the limbs; the colour of the face was unchanged. When he was almost under, that is, when the conjunctival reflex had nearly disappeared, and without any warning, the quiet breathing suddenly ceased, though the chest movements continued. I removed the apparatus, pushed forward the lower jaw, but could neither hear nor feel any air current. Meantime the colour of the face was slowly becoming an ashy grey colour, while the pulse continued regular and of fair volume. Then I depressed the lower jaw, whose muscles were quite lax, and pulled the tongue well out with forceps; still no entry of air. I also passed my finger to the back of the throat, but found nothing that could obstruct the air passage. Concluding that there was spasmodic closure of the glottis, I hastily sent the attendant nurse into the theatre for Mr. Barling and for tracheotomy instruments. Mr. Barling explored the pharynx with the forefinger, but found nothing until with some effort pushing his finger beyond the epiglottis he felt its tip entering the larynx, which was firmly closed. After a little steady pressure the spasm relaxed. He withdrew his finger, air entered, and the patient very quickly recovered colour, and began to show every sign of rapidly-returning consciousness. All this happened in two or three minutes at the most, and all the while the chest movements continued. When the patient had regained colour the back of the throat was swabbed out, but only a small plug of mucus was removed. There had previously been no evident secretion.

Waiting until the patient had practically recovered consciousness I administered the A.C.E. mixture on Silk's metal hospital inhaler, and had very little trouble afterwards. Early in the operation I tentatively added some ether to the mixture when the patient was not very deeply under, and he at once began to breathe stridulously. Thereafter I kept him generally deeply under the influence of the A.C.E. mixture until the end of the operation, the pupils being moderately dilated, with pulse and respiration regular. Once or twice only was there a little very slight phonation. The colour was as before the anæsthetic. When the operation, which took about three quarters of an hour, was finished, the patient came round very slowly, and as he showed no sign of consciousness in about 15 minutes, I opened the mouth with the gag and put my finger down his throat and about the epiglottis. This excited some reflex straining and some laryngeal spasm for a minute or so and then he vomited a few ounces of dark green bilious fluid and frothy mucus. It was more than one hour before he came properly round. As regards the operation, his wound healed by first intention and he did excellently. On February 11th, after he had been quietly recumbent in bed for a few days, I examined his heart with Dr. Bernard Bostock, the House Physician, and we found no thrill or presystolic murmur, but a well marked, soft, mid-diastolic murmur.

On March 1st, when the patient was up and about the ward, I examined him again. He said he felt "quite well," denied having had rheumatism, or anything else the matter with him that he knew of, but admitted that he was "short of breath" at times, and tired. On examination in the erect position (he had previously been sitting) I found his heart condition as on February 11th, but after getting him to walk about a dozen yards sharply I found a well-marked thrill and presystolic murmur. After he had been standing still for two or three minutes this was replaced by the mid-diastolic murmur. Thus the mid-diastolic murmur was indicative of less heart strain and better compensation. The patient eventually left the hospital cured of his appendicitis.

Curiously enough, Mr. Barling two or three days before this event had said that in a large experience of operations and anæsthetics he had never yet seen a case of really serious laryngeal spasm during the administration of an anæsthetic. I myself have never before or since observed any condition like this. I had, in choosing the anæsthetic for this case decided to give either the A.C.E. mixture—having in mind the below-mentioned cases quoted by Dr. Hewitt—or gas and ether; but unluckily I preferred the latter. To my mind the laryngeal spasm in this case might have been due to one of two causes. Either a direct irritant effect of the ether vapour of a certain strength, acting on a perhaps particularly sensitive laryngeal tract; or later on in the narcosis the addition of ether to the A.C.E. mixture caused stridor. Whether the sensibility of the mucous membrane to irritation was at all due to the cardiac condition is doubtful. Dr. Frederick Hewitt, in his admirable book on anæsthetics, quotes three cases of mitral stenosis recorded by Mr. Penberthy in which the A.C.E. mixture had been given with the best results. In one of these cases it is noted that "the patient had formerly taken ether with a nearly fatal result." I do not understand why certain patients with compensated mitral stenosis should not be able to take ether, unless their tendency to bronchitis has possibly something to do with it. In another case of mitral stenosis, a girl aged 18, whom about six months later I had to anæsthetise, I gave the mixture of ether 2 parts, chloroform 1 part (E, C₁), by means of a Clover's inhaler without the bag, and had no trouble. Or the laryngeal spasm might have been due to a plug of mucus suddenly inspired into the glottis. Mr. Barling rather favoured this view, though personally I incline to the