B_1 excreted and the data subsequently recorded for the placenta these data are here summarized independently.

The placentae were collected as soon as possible after labour and weighed without cord and membranes. The fresh tissue was then fed direct to rats, usually 6 for each placenta, at a dose level of 7½ g. a rat. The concentrations of vitamin B_1 in the placenta were then estimated as described above. The resulting figures are plotted, again on a logarithmic scale, in Fig. 2, and summarized together with the weights in Table II. Although there was no significant correlation between the weight of the individual placenta and the concentration of vitamin B_1 in it, in both cases, as with the urinary excretion of the vitamin, the average readings for the group of eclamptic patients are very significantly below those for the normal group. The t-test shows that the odds against the chance occurrence of differences as large as those observed are many thousands to one in the case of the placenta weights, and millions to one in the case of the vitamin B_1 concentrations.

None of the other clinical groups differs very significantly from the normal in its vitamin B_1 concentration; a difference as large as that recorded between the average placenta weights in the pre-eclamptic and normal groups would occur by chance on rather less than 1 in 40 occasions, but since the scatter of the mean weights in the first 4 clinical groups is not nearly so exceptional we prefer not to stress this particular contrast. A similar remark applies to the difference between the average vitamin B_1 concentrations in the oedema and normal groups.

TABLE II.—*Placentae*

Clinical Group	No. of Cases	B_1 per 100 g. of Placenta			Mean Placenta Wt.	
		Mean Log.	Corr. B_1 (I.U.)	t	g.	t
Normal ..	34	1·288	19·4	—	539	—
Hypertension	8	1·297	19·8	0·17	542	0·02
Oedema ..	2	1·508	32·2	2·19	367*	1·34
Pre-eclampsia	7	1·329	21·3	0·72	429	2·32
Eclampsia ..	5	0·772	5·9	7·81	274	5·54

* 1 case only.

Note.—The values of t given above are those appropriate to testing separately the significance of the differences between the group means and the mean in the normal group. They are based on 50 degrees of freedom.

Summary

A series of 106 cases of pregnancy among hospital populations has been examined.

It was found (1) that in eclampsia the amount of vitamin B_1 excreted in the urine on admission to hospital is significantly lower than in normal pregnancy; and (2) that the concentration of vitamin B_1 in the placenta is also significantly below that of the placenta from normal cases.

In view of these findings and the occurrence of oedema and suppression of urine in eclampsia, offering a striking similarity to the clinical picture of beriberi, it is suggested that vitamin B_1 therapy might be beneficial to such patients.

We wish to thank Dr. Allen Daley, Chief Medical Officer of the L.C.C., for granting us the facilities for this investigation and for permission to publish its results.

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J. G. Strohm (*Urol. cutan. Rev.*, 1941, **45**, 770), who records his observations on 429 cases of carcinoma of the prostate in various hospitals in Portland (Oregon), states that one-fifth of the male patients who seek relief for obstruction of the vesical neck have this disease. In the majority of cases growth begins in the posterior lobe. Skeletal metastases are found in the pelvis, sacrum, lumbar vertebrae, femur, and dorsal spine, in the order named. Bilateral sciatica is almost indicative of cancer of the prostate, and even unilateral sciatica should be regarded with suspicion. The two most typical symptoms are frequency and difficulty of micturition. The age of Strohm's cases ranged from 17 to 92. Treatment by female hormones relieved the pain of bone metastases to some extent.

SUBARACHNOID HAEMORRHAGE IN IDENTICAL TWINS

BY

JOHN G. O'BRIEN, M.B., B.Ch., B.A.O.

The well-known similarity of physical characteristics in identical twins and the nature of their origin suggest that they should be liable to the same diseases. In particular, those pathological processes which depend on congenital anomalies of structure, such as bicuspid aortic valve or lack of tunica media at arterial junctions, might be expected to affect both rather than one of a pair of uniovular twins. Examples of this must of course be rare, and no instance of subarachnoid haemorrhage has been reported, so far as I have been able to ascertain. The case of an identical twin treated for this condition in the East Suffolk Hospital, Ipswich, aroused particular interest because of this possibility, and I consider it worth putting on record, despite the interval that has elapsed. On inquiry it was found that his twin brother had died some years earlier in very suggestive circumstances. As there are rather unusual features about the case it is perhaps advisable to give the history in full.

Clinical and Pathological Record

The patient was employed by a Suffolk farmer pulling sugar beet. He is said to have been an excellent worker, cheerful and intelligent, and never to have complained in any way. On November 26, 1938, he was found lying in an empty house, and, according to the relieving officer who saw him, there was a history of inebriation the previous day. His condition was ascribed to this, coupled with cold and exposure. On admission to the local infirmary he was found to be in an exhausted condition but conscious. He was extremely quiet, but complained of severe headache. The temperature was 99.4°, the pulse 68, and the respirations 26. There was no apparent paralysis—a negative observation which is important in view of subsequent findings.

Next day limpness of the left arm was noticed and headache still continued to be severe. Heavy albuminuria occurred on the third day, and transfer to the East Suffolk Hospital was arranged. He was admitted under Dr. Ronald Jones on November 29. When seen the patient was very drowsy and speech was slurring. The nurse who had accompanied him stated that the drowsiness had been increasing gradually. The following were the findings on examination: head retracted and rotated to the left, immobility of left arm and leg, twitching of left leg, rigidity of neck, pupils equal and reactive, disks flat, left facial weakness of upper neurone type, tongue deviated to left on protrusion, abdominal reflexes absent, limb reflexes absent, positive Babinski on left. There were hypotonia of the limbs, more marked on the left, and relative anaesthesia of the left side as a whole. Lumbar puncture revealed a uniformly blood-stained fluid at a pressure of over 400 mm. and, on centrifuging, the specimen yielded a yellow supernatant fluid. The blood pressure was 165/90.

Subarachnoid haemorrhage was diagnosed and daily lumbar punctures were started. The cerebrospinal fluid became free of visible blood in a fortnight, its pressure fell to 220 mm. and the colour became deep yellow. The patient began to take an interest in his surroundings, though slight headache and head retraction still remained. The paralysis was unchanged. Improvement continued for a further fortnight, when the fluid was a translucent yellow and the manometric reading 200 mm.

Apart from the left hemiplegia, the case up to this point had followed a comparatively normal course. Hemiplegic symptoms, however, are not uncommon in subarachnoid haemorrhage. There is no reason to suppose that, had no other condition supervened, the patient would not have survived and ultimately recovered some degree of power in his leg and possibly his arm. On the following day, however, he was prostrated with violent headache and pyrexia of 101° F. The C.S.F. pressure rose to over 400 mm. and the fluid itself became turbid. It yielded meningococci in culture, and gave a positive meningococcal pre-

cipitin reaction. No other case of cerebrospinal fever occurred in the hospital during the period immediately before and after this infection. Despite treatment, death occurred a week afterwards. On one occasion *B. coli* was found in a specimen, but as this finding was not repeated despite careful search and culture it may be regarded as a contaminant.

Post-mortem Findings.—A necropsy performed by Dr. E. Biddle, pathologist, revealed a very interesting condition. The brain was congested and oedematous, with thick pus over the base. In the middle of the right hemisphere beneath the Rolandic area was a haemorrhagic cyst about 4 cm. in diameter, with a pigmented wall. The contained blood was, however, only about three to seven days old. Near the origin of the left middle cerebral artery was a thrombosed aneurysm about 1 cm. in diameter, and adhesions and pigmentation in the surrounding tissues pointed to leakage. Dr. Biddle suggested that a rise in blood pressure consequent on the original subarachnoid haemorrhage caused rupture of a branch of the right middle cerebral artery. This supposition explains the history of the headache and drowsiness with collapse antedating the onset of paralysis by about twenty-four hours. It is unfortunate that in this initial phase a lumbar puncture was not performed, as blood in the C.S.F. at this stage would have indicated an uncomplicated subarachnoid haemorrhage. It may be noted that the localized effusion was in the position in which apoplectic haemorrhages usually occur. No atheromatous or arteriosclerotic changes in the vessels were observed. The apparent age of the blood in the cyst might have been due to an addition to its contents during the period of increased pressure after the onset of meningitis. The findings in this case may afford a clue to some cases of hemiplegia following rupture of a congenital intracranial aneurysm.

The Case of the Twin

It was found on inquiry that the deceased's twin brother had been of similar weight, height, and appearance when alive. He had died eight years previously while on holiday. After a breakfast at 9 a.m., which he seemed to enjoy, he proceeded to the tennis court with his wife. While playing he complained of severe headache and retired to bed. He either dozed or was unconscious during the afternoon. In the evening, after taking some brandy, he became violently sick, and death occurred next morning. For some unknown reason a doctor was not called in until after death, and a necropsy was not performed.

The sudden onset of headache during exertion in a previously healthy adult of 26, followed by coma, and ending in death within twenty-four hours (plus a bout of vomiting, which might, however, have been due to the brandy), might almost be considered pathognomonic of subarachnoid haemorrhage. The following is the relevant extract from the "Register of Deaths" regarding the case: "Natural causes—brain condition either that of brain abscess ruptured into a ventricle or spontaneous haemorrhage of a congenital flaw in a brain artery."

It will be noted that ruptured brain abscess is given pride of place. No primary condition such as otitis media or sinusitis which might give origin to an abscess is mentioned, however, and the deceased's father states that he had been in good health before the catastrophe occurred. It must also be remembered that the certifying doctor did not see the patient until after death. The weight of evidence would seem to favour the "flaw in a brain artery," though in the absence of a necropsy there cannot, of course, be any absolute assurance on the point.

Discussion

The occurrence of subarachnoid haemorrhage in identical twins raises the interesting possibility of surgical intervention in the case of the second or surviving twin, based on the post-mortem findings on the first. The combination must be so rare, however, that this will probably remain a matter of purely speculative interest. In connexion with the case as described there are a few points of interest which have not yet been discussed. The heavy albuminuria noted on the third day is an occasional occurrence in subarachnoid haemorrhage and does not necessarily indicate a renal origin of the vascular condition. It might be mentioned that glycosuria may also occur and give rise to an erroneous diagnosis of diabetes.

The treatment of this condition has not yet been standardized, and the repeated lumbar punctures carried out in treating the present case would, in all probability, not receive unqualified approbation. Daily punctures were performed until the fluid became free of visible blood, in the belief that (1) they tend to interrupt the vicious circle of haemorrhage → cerebral anaemia → rise in blood pressure → more haemorrhage; (2) they reduce the total fibrinogen in the C.S.F., and any replacement from the normal source reduces it relatively, with a resultant diminished danger of clot formation. The movement of fluid resulting from lumbar puncture also helps in this direction. One of the complications of the condition is clotting of the edges of a haemorrhage effused over the vertex, with the formation of a "pancake haematoma" in the centre of which bleeding is still taking place, with pressure on the cerebral hemisphere and possibly hemiplegia. Spinal drainage will not relieve this once the condition is established. (3) They afford symptomatic relief.

In connexion with the vicious circle referred to, it might be of advantage to recount the sequence of events in intracranial haemorrhage as pictured by physiologists, more especially as it is also the basis of the explanation suggested by Dr. Biddle. The brain, with its membranes, blood vessels, and C.S.F., completely fills the cranium. If the volume of this latter is encroached upon by the addition of free blood (or any other space-occupying mass) pressure is exerted on all the contents. Of these, the blood vessels alone have free and direct exit for their contents, and so bear the brunt of the compression. The blood available to the nervous tissue is thus directly squeezed out, and, moreover, circulation through the brain is hindered somewhat as the passage of water through a soft rubber hose is hindered by pressure with one's foot. The net result is a cerebral anaemia with an accumulation of CO_2 which stimulates the vasomotor centre to activity and thus raises the blood pressure. This will tend to increase the bleeding and initiate the sequence again. The process if unchecked may go on to paralysis of the vital centres and death.

The removal of C.S.F. eases the strain on the circulation by reducing intracranial tension and thus tends to interrupt the vicious sequence. There is of course a danger that reduction of the C.S.F. to any marked extent before the circulation has adjusted itself to the improved conditions may increase the strain on any clot which has formed at the rent in the vessel wall, and perhaps dislodge it. The importance of this is a moot point, and is open to discussion. Obviously the more slowly the fluid is withdrawn the less likely is this catastrophe to occur.

In the case under discussion rupture of a congenital aneurysm was probably the first event. It is suggested that rupture of an intracerebral vessel, perhaps the "artery of haemorrhage," occurred about twenty-four hours afterwards, with production of hemiplegia. This was in the situation in which rupture occurs in hypertension, and was probably due to a rise in blood pressure following on the subarachnoid haemorrhage. Hemiplegia was already apparent when the lumbar punctures were begun, and thereafter a gradual improvement set in until meningitis supervened. Should this suggested sequence have been the actual train of events there is a distinct possibility that lumbar puncture in the initial phase might have prevented the secondary rupture and hemiplegia.

The only fact which does not fit in with this hypothesis is the apparent age of the blood in the cavity. This, as already suggested, might have been added to the cyst during the course of the meningitis. The alternative is that the

cyst was formed during the meningitis and was entirely unrelated to the hemiplegia, the occurrence of which would then be unexplained. As for the infection itself, one can only regard it as a fortuitous event which proved to be the last straw for the patient.

The occurrence of these three clinical entities—subarachnoid haemorrhage, intracerebral haemorrhage, and meningitis—in any one patient is such a rare event that it is interesting to speculate what the odds against their happening in an identical twin are—an astronomical figure, surely! That the case should have occurred at all is an example of the interesting possibilities that sometimes materialize during the course of medical practice.

I should like to express my thanks to Dr. Ronald Jones for permission to publish this case as well as for his criticism and advice, and to Dr. Eric Biddle for the use of his post-mortem notes on the subject.

UREA AND ITS EFFECT ON TUBERCLE BACILLI

BY

Prof. S. L. CUMMINS, C.B., C.M.G., M.D.

Urea has been shown to have a marked beneficial effect in the treatment of septic wounds as well as to possess certain physiological properties in regard to proteins. Spiro has been quoted in relation to the latter, but I have not been able to have access to his paper, dated 1900. Ramsden, in 1902, showed that it acted as a "*substance sensibilisatrice*," rendering proteins more prone to zymolysis, conversion into acid- or alkali-albumin; as a protective substance, since coagulable proteins are not heat-coagulable in its presence but reacquire their coagulability when the urea is removed by dialysis; and as a solvent. He added that "in a saturated urea solution no putrefaction ever takes place."

Symmers and Kirk (1915) made a powerful claim for treatment of septic processes by crystalline urea. Kirk, after giving striking examples of its successful application, pointed out, however, that the wounds should be kept tightly closed by covering the urea with some dry protective material such as oiled silk or by suturing, as a "dry dressing on top of the urea absorbed the solution and prevented its action on the tissues." Symmers, dealing with the problem from the bacteriological point of view, showed that strong concentrations of urea were bactericidal and bacteriostatic. He showed, further, that urea would kill bacteria in the presence of blood and other protein substances.

One of Symmers's experiments—a very striking one—may, however, have given rise to some misunderstanding and deserves to be carefully considered. He took two tubes of tuberculous sputum. To one of these he added urea and the other he left as a control. From the tube treated with urea a culture was made after 15 minutes from which only 3 colonies grew. From a further culture put up after 30 minutes there was only one colony. From the control tube there was abundant growth on agar. Anyone reading this account in a hurry might imagine that it was intended to convey that tubercle bacilli had been killed, but this was not the fact or the intention. The tuberculous sputum had been chosen because it afforded a good example of a badly contaminated sputum. Its culture after 15 minutes and half an hour showed that the urea had sterilized it or at least had gone very far towards sterilizing it in a very short space of time, whereas a culture from the control sputum gave an abundant growth on agar. The experiment was not intended to prove the sterilizing effect of urea on tubercle bacilli, but to show its effect on putrefactive organisms.

The Experiment

It occurred to me, therefore, to try the effect of urea on the tubercle bacillus itself as exemplified by a pure culture. Two cultures were obtained from Prof. W. H. Tytler of the Welsh National School of Medicine. One of these failed to grow either with or without urea, and was therefore put aside as useless for the tests. The other, labelled "Pleural Fluid 22924" and dated Nov. 8, 1941, was emulsified in sterile water to a dilution of about 5,000 million bacilli per c.cm., the number being judged by the opacity of the fluid but not counted.

On Dec. 30, 1941, in each of 4 sterile test-tubes was placed 1 c.cm. of this suspension of tubercle bacilli, urea being added as follows:

Tube I :	Sat. sol. urea	1 c.cm. of tubercle suspension
,, II :	,, ,, ,, /2	1 ,, ,, ,,
,, III :	,, ,, ,, /4	1 ,, ,, ,,
,, IV :	,, ,, ,, /8	1 ,, ,, ,,

At the same time 1 c.cm. of tubercle suspension was put up with 1 c.cm. of distilled water, two test-tubes being thus suspended so as to have two "controls."

All 6 tubes were then transferred to the incubator at 37° C. and left for 48 hours. At the end of this time each tube was removed and 0.5 c.cm. of the contents placed on a "bottle" of Löwenstein-Jensen medium, the screw cover being well fixed and the bottles placed in the incubator at an angle close to the horizontal. After a week they were replaced vertically, the surface being dry.

On Feb. 9, 1942, the culture tubes were examined and found to show growth of tubercle bacilli as follows:

Tube I :	Sat. sol. urea ..	T.B. susp. ..	No growth
,, II :	,, ,, ,, /2 ..	,, ,, ..	,,
,, III :	,, ,, ,, /4 ..	,, ,, ..	+
,, IV :	,, ,, ,, /8 ..	,, ,, ..	++
Control :	Aq. dest.	,, ,, ..	+
,,	,, ,, ...	,, ,, ..	++

It should be recalled that the saturated solution of urea had been diluted in each tube by an equal volume of bacillary tubercle suspension, so that the final cultures were made with half the strength in each tube.

Conclusions

The experiment shows that urea in dilutions of half saturation and one-fourth saturation completely kills off the tubercle bacilli from a thick emulsion in 48 hours. In an eighth and a sixteenth dilution, however, it is powerless to kill, though it is significant that the growth was much less on Tube III than on Tube IV. The phenomenon seems to be just the same as that noticed by W. J. Wilson (1906) with coliform and other bacteria.

Seeing that urea either in the pure state or in saturated solution is harmless to the tissues and that it not only kills tubercle bacilli in very large numbers but also destroys septic secretions and ordinary saprophytes as well as pathogenic germs, it would appear very suitable as a dressing for tuberculous ulcers and even, perhaps, for cavities close to the pleural surface where adhesions have made these accessible or small tuberculous empyemata. In the treatment of tuberculous ulcers, however, where the crystalline urea was being used, it should be protected from absorption by the dressings by the interposition of oiled silk or some similar material between the urea and the dressings.

It is to be noted that Stonham (1941) reported favourably on urea in the treatment of septic wounds and that Muldavin and Holtzmann (1938) obtained with it excellent results in infected cases.

Good accounts of the physiological and therapeutical uses of this substance may be found in articles by Gurchot and McCawley (1940) and Holder and MacKay (1939).

My best thanks are due to Prof. W. H. Tytler for the culture used, and to Lieut.-Col. A. S. M. Winder, R.A.M.C., and Sgt. C. Neill, R.A.M.C., for much kind assistance.

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