CHEMOTHERAPY AND SEROTHERAPY IN CEREBROSPINAL (MENINGOCOCCAL) MENINGITIS

AN ANALYSIS OF 3,206 CASE REPORTS

BY

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Cerebrospinal (meningococcal) meningitis, usually known as cerebrospinal fever, became compulsorily notifiable throughout England and Wales on Sept. 1, 1912; previous to that date the disease had been notifiable only in certain districts. The prevalence from 1913 onwards is shown in the following abridged table of notifications, with deaths in parentheses:

TABLE I

1913	1914	1915	Av. 1916-20	Av. 1921-5	Av. 1926-30	Av. 1931-5	1936	1937	1938	1939	1940
305 (332)	315 (194)	3,712 (2,203)	1,000 (908)	371 (343)	516 (490)	1,593 (988)	994 (635)	1,140 (698)	1,288 (652)	1,500 (514)	12,771 (2,584)

Between the peak years 1915 and 1940 the smallest annual number of notifications was 301 in 1923, and the largest 2,157 in 1931. The prevalence remained at a low level from 1920 to 1929, when it began to rise until 1931-2. A decrease thereafter was followed by a steady increase, and in the Chief Medical Officer's Annual Report for 1938 the statement was made that as since the epidemic period in 1931-3 the number of notifications had not fallen to so low a point as after the 1915-17 epidemic, and as the number of Group I infections appeared to be increasing, the probability that we were approaching another period of epidemic prevalence could not be disregarded. The suspicion was confirmed in 1940, and to a degree beyond expectation.

It is possible, however, that in the second and third quinquennia in the table the annual numbers of notifications from which the averages are derived do not represent the true prevalence, for it is precisely in those years of minimal notification that the deaths were proportionately high and in some years even exceeded notifications. On the other hand, as was suggested in a previous Annual Report, it may be that in years of high prevalence, when medical practitioners are on the look-out for the disease, a larger proportion is notified than in years of low prevalence, when cases occur sporadically and are more easily overlooked. Also, as pointed out by Reece (1917), in times of prevalence cases of anomalous disease are more likely to be attributed to cerebrospinal fever than are genuine cases to be overlooked. Probably, then, in the years under review the deaths and not the notifications would be the proper gauge of prevalence.

Fatality Rate.—In the light of these views the fatality rates from 1913 to 1930 can only be approximate. Nevertheless, two conclusions can now be formed: first, that, owing to the almost invariable recourse to bacteriological aid in diagnosis, notification has become more trustworthy as an index of prevalence in recent years; secondly, that there has of late been a steady and real decline in fatality. For instance, in the period 1927-34, comprising four years of low prevalence succeeded by four of high, the average fatality of the first four years was 95% and of the second four 61%. Even allowing that the former figure may be too large through being related to a period of under-notification and the latter figure too small on account of the opposite reason, there is still room to believe that decline took place and, further, to regard a contemporary improvement in the administration of antimeningococcus serum as a factor in the decline. Again, in the years 1935-9 as the annual numbers of notifications increased so the fatality rates decreased, being successively 69.8, 63.8, 61.2, 50.6, and 34.2. The conspicuous drop in the last two years was due to the introduction of the drugs of the sulphonamide series in the treatment of cerebrospinal fever.

Distribution.—In the period 1913-39 the disease was widely spread, here and there assuming the character of epidemicity, as in the West Riding of Yorkshire in 1931-2, the counties of

Lancaster, Durham, Derby, and Nottingham in 1932, and in Wrexham district in 1939.

Prevalence in 1940.—The alert was sounded early. In the second week in January the number of notifications rose from 53 to 107, and in the first nine weeks of the year the numbers were successively 53, 107, 144, 184, 299, 406, 557, 585, and 617. From the ninth week (ended March 2) they declined irregularly to 106 in the first week of September. Thenceforward there was a rise, which continued with slight remissions to the end of the year and into 1941 to a maximum of 406 in the week ended Feb. 22.

Distribution in 1940.—The disease prevailed impartially throughout the country; no county in England or Wales escaped, and there were no "dramatic local outbursts." London, which in 1915 suffered severely in proportion to the rest of the country, in 1940 returned only 880 notifications out of the total of 12,771. No doubt this was due to the absence, through evacuation, of a substantial proportion of young persons—those, in fact, in the most susceptible age groups. At the peak of the prevalence (week ended March 2) sixteen counties returned 15 or more notifications, the highest being Lancaster 52, Southampton 51, and Glamorgan 37.

Character of the Disease.—This was of the usual severity. Quite 60% of the case reports analysed below had been noted by the physicians in charge as severe or very severe, and fulminating cases unresponsive to the promptest treatment were not rare. The low fatality rate for the year—20.2%—cannot therefore be discounted by any suggestion that the disease was of a milder order than formerly.

Serum Treatment

In 1930 it became apparent that the results of serum treatment were not proving so satisfactory as those obtained, for instance, among military cases in 1917-18. It was suggested that the cause was that the serum available had been prepared from old strains of meningococcus or strains isolated in inter-pandemic times, and so might lack antibodies to the organisms responsible for the current outbreak. Another suggestion, advanced by Gordon (1920), was that the serum was deficient in anti-endotoxin. Arrangements were therefore made by the Ministry in 1931 whereby manufacturers of serum were provided with strains of meningococcus procured from current cases of the disease, and reports on the results of treatment by this new "current" serum were invited from medical officers of health, hospital medical officers, and medical practitioners (Reports on Public Health and Medical Subjects, No. 65). This was followed in 1932 by the issue of a *Memorandum to Medical Officers of Health* urging the prompt administration and repetition of adequate doses of serum. From an analysis of the reports received at the Ministry by Dr. E. L. Sturdee in the four years 1931-4 the following figures were extracted. In 382 cases untreated by intrathecal injections of the current antimeningococcus serum the fatality was 61.8% (Sturdee, 1936). In 2,279 cases treated by intrathecal injections of the current serum the fatality was 36.6%. Of the 2,279 cases, 988 that were treated with the current serum on the lines of the recommendations in the Memorandum gave a fatality of 27.9%. Of these 2,279 cases the ages were known in 2,274, and among these the fatality was as follows:

TABLE II

Age Group	Fatality (%)
Under 1 year	67.2
1 and under 5	38.6
5 " " 15	22.7
15 " " 20	28.1
20 " " 30	35.2
30 " " 40	45.2
40 " " 50	58.2
50 and over	71.4

Chemotherapy

In 1935, when prontosil was introduced, a new era dawned in the fight against microbic disease. From prontosil was derived sulphanilamide, and when it was found that prontosil was partly converted in the body into sulphanilamide and also that it passed more slowly from the blood into the cerebrospinal fluid than sulphanilamide the latter became the drug of choice. Banks (1938) reported his results of treatment with serum alone, with serum and sulphanilamide, and with sulphanilamide alone. In 38 cases treated with large doses

of serum intravenously and intrathecally the fatality was 16% ; the method was relatively difficult and laborious, and the nursing complicated for several days. In 59 cases treated with both serum and sulphanilamide the fatality was 11.8% ; recovery was very rapid and the nursing relatively easy. In 16 selected cases of favourable age-grouping treated with sulphanilamide alone there were 15 rapid recoveries. But Whitby (1938) found that another of the sulphonamide derivatives labelled sulphapyridine (M & B 693) was more effective against the pneumococcus than sulphanilamide and equally potent against the meningococcus, and also was less toxic to the patient. This was a great advance, as sulphapyridine can be promptly administered to a case of purulent meningitis while the bacteriological report as to pneumococcal or meningococcal origin is awaited. Banks (1939), reporting on further experience with serum, sulphanilamide, and sulphapyridine, stated that there was no evidence in favour of auxiliary treatment with serum, that sulphanilamide must be given in doses high enough to maintain a certain concentration of the drug in the cerebrospinal fluid for eight or nine days, but that a smaller dosage of sulphapyridine might prove to be successful and that the oral route could be used throughout in most cases.

In consequence of the encouraging results obtained by chemotherapy the Ministry issued in March, 1940, a Memorandum (234/Med.) briefly summarizing the modern views on the treatment of cerebrospinal fever, and giving an account of the dosage and procedure recommended by Banks. The Memorandum also stated that although there appeared to be no convincing clinical evidence that the use of serum was necessary, even as an adjuvant to chemotherapy conducted on the lines given in the Memorandum, nevertheless some recent animal experiments suggested that better results might be obtained by combining the two forms of treatment. Thus, though there was general agreement that Group I and Group II meningococci were equally susceptible to sulphanilamide or sulphapyridine and that the use of these drugs marked a great advance in the treatment of cerebrospinal fever, it was uncertain whether the combined use of either of the drugs with serum was preferable to the use of the drug alone. Jordan *et al.* (1940) obtained far better results when either immune serum or antitoxin was combined with sulphapyridine. Harries (1940) combined the drug treatment with antitoxin in severe cases only. Williams and Brinton (1940), following the practice of Banks, treated 45 consecutive cases with sulphapyridine alone ; all the cases recovered and remained free from sequels. These cases, however, were among very fit adults, presumably in favourable age groups.

To secure information on the results of treatment during the high prevalence of cerebrospinal fever in 1940 the Ministry sent in April of that year a letter to the medical officers of health of certain large boroughs throughout the country requesting particulars of cases treated in hospital since the beginning of the year. A form for each case was provided showing the nature of the particulars desired ; these included the name of the drug and the amount and hour day by day of each dose of the drug, and of serum if used. The response from medical officers of health and medical officers in charge of isolation and other hospitals was generous, and it is gratefully acknowledged. More than 60 hospitals contributed.

In estimating the fatality rate in a large series of cases treated by serum, Sturdee (1936) excluded deaths due to intercurrent disease or occurring within 24 hours of the first administration of serum. In the present analysis, though serum was not given alone, all cases (approximately 130) were excluded that did not survive more than 24 hours after admission to hospital ; this seemed equitable in comparing the results of the methods of treatment—chemotherapy combined with serum, and chemotherapy alone. The total number of cases for analysis, then, was 3,206 ; of these 849 were treated by the combined method and 2,357 by chemotherapy alone, and the fatality rates of these two classes are given in Tables III and IV.

The antimeningococcus sera and antitoxins used were designated "Burroughs Wellcome and Co.," "Parke, Davis and Co.," "Lister," "Lilly," "Mulford," "Sharp and Dohme," "Lederle," and "New York State." Most of the cases in Table III were treated by sulphapyridine orally and polyvalent serum intrathecally. Occasionally in the treatment of a case the sequence of oral administration was interrupted by

parenteral injections of sulphapyridine (soluble M & B 693) or of soluseptasine (a sulphonamide). In the same manner changes were made to sulphonamide (? sulphanilamide) in 7 cases,

TABLE III.—*Fatality Rates in 849 Cases treated in Civilian Hospitals by Chemotherapy and Serum, and Surviving more than 24 Hours after Admission*

Age Groups	Cases		Deaths		Fatality %		Age-group Fatality %
	M	F	M	F	M	F	
Under 1 year ..	26	14	9	4	34.6	28.5	32.5
1-2 years ..	27	18	6	2	22.2	11.1	17.7
2-3 " ..	31	18	3	3	9.6	16.6	12.2
3-4 " ..	29	25	5	7	17.2	28.0	22.2
4-5 " ..	16	12	2	1	12.5	8.3	10.7
5-15 " ..	78	76	7	6	8.9	7.8	8.4
15-25 " ..	115	69	3	5	2.6	7.2	4.3
25-45 " ..	145	82	22	10	15.1	12.1	14.1
45-65 " ..	25	31	7	9	28.0	29.0	28.5
65 and over ..	7	5	3	3	42.8	60.0	50.0
All ages ..	499	350	67	50	13.4	14.2	13.8

TABLE IV.—*Fatality Rates in 2,357 Cases treated in Civilian Hospitals by Chemotherapy alone, and Surviving more than 24 Hours after Admission*

Age Groups	Cases		Deaths		Fatality %		Age-group Fatality %
	M	F	M	F	M	F	
Under 1 year ..	102	72	24	15	23.5	20.8	22.4
1-2 years ..	89	54	14	5	15.7	9.2	13.3
2-3 " ..	89	54	8	11	8.9	20.3	13.3
3-4 " ..	45	50	4	7	8.8	14.0	11.5
4-5 " ..	39	37	4	1	10.2	2.7	6.5
5-15 " ..	236	218	12	13	5.0	5.9	5.5
15-25 " ..	330	159	9	3	2.7	1.8	2.4
25-45 " ..	374	197	16	22	4.2	10.1	6.6
45-65 " ..	82	113	13	29	15.8	25.6	21.5
65 and over ..	9	8	5	4	55.5	50.0	52.9
All ages ..	1,395	962	109	110	7.8	11.4	9.2

prontosil in 3, and sulphathiazole (thiazamide) in 3, and in 11 cases sulphonamide (? sulphanilamide) alone was combined with the serum.

Group I serum was given in 29 cases, and Group II serum in 2 cases, in addition to polyvalent serum. In 85 cases meningococcus antitoxin was given, mainly instead of, and sometimes in addition to, polyvalent serum ; the use of antitoxin was confined to one or two hospitals. Meningococcus vaccine was administered in 3 cases.

The drug most often employed in Table IV was sulphapyridine, usually by the mouth and sometimes, in addition, intramuscularly or intravenously ; sulphanilamide, soluseptasine, and sulphathiazole were also used, but not often enough for separate analysis of effect in treatment.

The salient points in Table III are: (a) the low fatality rate for males in age group 15-25 ; (b) the nearly equal sex fatality for all ages, 13.4 and 14.2 ; (c) the low total fatality rate of 13.8 ; (d) the almost unbroken curve of the age-group fatality, falling from infancy to adolescence and then rising to old age. We have no figures of the same age groups to consult, but this was in general the curve in former times.

Table IV, in comparison with Table III, presents a more regular curve of fatality, from infancy downwards to adolescence and rising to old age ; and, except in the age groups 3-4 and 65 and over, the fatality rates are substantially lower than in Table III. The fatality at all ages of cases treated by chemotherapy alone was 9.2%, as contrasted with 13.8% among cases treated by chemotherapy combined with serum. In Table IV the very low rate—2.4%—in the age group 15-25 is particularly notable.

Presence of Meningococcus

It is satisfactory to record that out of the total of 3,206 cases the cerebrospinal fluid was examined for the meningococcus in 2,993 cases (93%), with a positive result in 2,727 (91%). The remaining 9% and the 213 cases in which there was no mention of examination were considered by the physicians in charge to be clinically beyond doubt. Of the 849 cases treated by chemotherapy plus serum the meningococcus was sought in 785 cases (93%) and found in 744 (94%). The corresponding figures for the 2,357 chemotherapy cases

were 2,204 (90%) and 1,983 (90%). The difference between the two classes in the percentages of search and success is not large enough to have a significance relative to the difference in their fatality rates, and it does not appear that the classes differed in the severity of their cases.

Meningococcal Groups

Brinton (1941) says that those who have had most experience of chemotherapy maintain that it has rendered treatment by serum as obsolete as routine spinal drainage. It was noted above that Group I serum was given in 29 cases, and Group II serum in 2 cases, in addition to polyvalent serum and chemotherapy. This proportion in 849 cases does not suggest that much reliance was placed on group sera, and perhaps we shall see group identification falling into desuetude. It is of special value, therefore, to have the opportunity of summarizing here the information gained from what may be the last large-scale inquiry into the incidence and distribution of the meningococcal groups.

Among the 849 chemotherapy-plus-serum cases (Table III) grouping was successful in 189, giving 172 Group I and 17 Group II—a proportion respectively of 91% and 9%. Among the 2,357 cases treated by chemotherapy alone (Table IV) grouping was successful in 489, giving 440 Group I and 47 Group II—a proportion respectively of 90% and 10%. Therefore, so far as was ascertained, the grouping in the two classes of treatment was practically identical. A few cases were reported either as "aberrant" or as reacting to the sera of both groups.

During the epidemic prevalence in the West Riding of Yorkshire in 1930-2 the presence there of Group I among the cases was reckoned at 94%. Among the 2,279 cases reported upon in the period 1931-4 the group was identified in 555, giving 441 Group I and 114 Group II—80% and 20% respectively. But though the period was one of comparatively high prevalence a large proportion of the strains examined came from non-epidemic areas in which Group II proved to be as common as, and in some even commoner than, Group I. The figures in 1940, coming from so many parts of the country where cerebrospinal fever was prevalent, again suggest that an increase of Group I is a factor in epidemicity, but we cannot define its rank of importance among other factors in 1940, such as the mixing of population, the aggregation of persons of susceptible ages, and the conditions of black-out aggravated by inclement weather.

The distribution of the groups was country-wide, contemporaneous, and collateral. As examples of Group I mention may be made of London, Birmingham, Bootle, Cardiff, Carlisle, Chesterfield, Colchester, Derby, Hull, Kettering, Manchester, Liverpool, Oxford, Norwich, Salford, Sheffield, Shrewsbury, and Sunderland. Group II appeared to be just as widely dispersed; London and most of the large towns referred to reported the presence of both groups.

Table V gives the percentage of Groups I and II found in each age period.

TABLE V

Age Group	Percentage of Meningococcal Group		Percentage of Cases not examined or Inconclusive on Examination
	Group I	Group II	
Under 1 year	18	4	78
1-2 years	24	1	75
2-3 "	22	4	74
3-4 "	28	1	71
4-5 "	16	3	81
5-15 "	22	3	75
15-25 "	17	2	81
25-45 "	16	1	83
45-65 "	13	2	85
65 and over	7	7	86

Severity of Meningococcal Groups.—It has been questioned whether there is a relation between the kind of meningococcal group and the severity of attack. A sampling of nearly 2,000 of the case reports was made with this point in view. Among the cases that could be termed severe or very severe the proportion of Group I was 19% and of Group II 2%; among the mild and moderately severe cases that of Group I was 18% and of Group II 1%. It will be remembered that the group proportions over all identified cases were 90% and 10%.

So in the cases under consideration Group II was at least as severe clinically as Group I.

Fatality of the Groups.—The fatality of Group II, moreover, was higher in all cases taken together; it is shown in Table VI.

TABLE VI

Description	Fatality %	
	Group I	Group II
All identified cases	9.7	12.5
Cases treated by chemotherapy and serum	12.2	23.5
Cases treated by chemotherapy alone	8.8	8.5

It appears, then, that in the cases reviewed Group II equalled Group I in severity and exceeded it in fatality. Something of this nature was hinted at in the Chief Medical Officer's Annual Report for 1931.

Comments

The aim of the Ministry was the collection of information on the results of treatment by chemotherapy, with reference particularly to the amounts and times of dosage as based on the experience of Banks and others, and embodied in the Memorandum of 1940. Many of the physicians filled up the case reports with exactness, giving the amount and hour of each dose of drug, and of serum if used, and added notes on the course of each case, the character of the attack, the response to treatment, and the occurrence of complications and sequels. Cerebrospinal fever is more deadly than deforming, yet its occasional withering effect on the most precious senses must seem at times only less tragic than death. An inquiry is being made into the occurrence and persistence of sequels and the relation of incidence to dosage. So far it appears probable that dosage was not a factor of great importance; and as to blindness and deafness, it is conceded that an early onset of grave damage to nerve cells may be irreparable by any size of dose in chemotherapy or by any form of treatment whatsoever.

It is desirable that the value of cerebral and lumbar puncture be defined, whether or no the procedure should be reserved for diagnosis. Instances of cisternal and ventricular puncture occur in the case reports, and some physicians performed frequent lumbar puncture for the relief of pressure while others never resorted to it for that purpose. In this connexion the opinion of Williams and Brinton (1940) may be quoted: "Neither the high cerebrospinal fluid pressure nor the absence of artificial drainage prevented the passage of sulphapyridine through the choroid endothelium into the cerebrospinal fluid. It seems that the concentration of sulphapyridine in the cerebrospinal fluid maintains a high level if the normal flow and absorption of fluid is undisturbed by repeated drainage. When adequate doses of sulphapyridine are given the disease can be effectively controlled without therapeutic lumbar puncture."

Another important question is whether the value of intramuscular injections of drugs is great enough to outweigh the risk of abscess and sloughing, and the consequent extra labour in nursing and delay in convalescence.

In no instance among the cases under review was a sulphamide injected into the theca. An account of two cases of paralysis of the lower limbs following the intrathecal injection of soluble sulphapyridine was published by Hunter (1940), and a group of four cases of myelitis after intrathecal injection of soluseptasine were reported to the Ministry in the same year.

It will be noted that there is a preponderance of males in the age groups 15-25 and 25-45. About 100 have been entered as non-civilians on the case reports, and it is possible that others have not been so identified; the excess of males is not to be regarded as an indication of greater susceptibility but of greater exposure to risk in living conditions due to war. At "all ages" of the cases the fatality rate of the females was higher (12.2%) than that of the males (9.3%). It may be that owing to circumstances a larger proportion of males received prompt treatment.

Summary

The fatality rate in 3,206 cases treated in hospital either by chemotherapy plus serum or by chemotherapy alone, and surviving more than 24 hours after admission, was 10.5%.

The rate in 849 cases treated by chemotherapy plus serum was 13.8%.

The rate in 2,357 cases treated by chemotherapy alone was 9.2%.

In the five years 1936-40 there was a steady decline in the fatality of cerebrospinal fever, the annual rates per cent. being successively 63.8, 61.2, 50.6, 34.2, and 20.2. In a series of cases treated in the period 1931-4 with serum of improved quality and administered suitably the rate was 27.9, but a decrease of the rate for the whole country did not occur until the introduction of chemotherapy; with the wider employment since 1938 of the sulphonamide derivatives the decline has been dramatic. In 1941 the rate was 19.5%, and in the first half of 1942 it was 19.5, as against 19.9 in the corresponding periods in 1940 and 1941. It is possible, therefore, that 1942 will show only a slight further decrease.

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A RARE CAUSE OF SEVERE GASTRO-INTESTINAL HAEMORRHAGE

WITH A NOTE ON ANEURYSM OF THE HEPATIC ARTERY

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The following case seems to merit publication as a rare cause of haematemesis: aneurysm of the hepatic arterial system is an infrequent condition, this instance constituting the 86th recorded. I am aware, however, of another case, still unpublished, in the National War Collection organized by the Medical Research Council. The present case appears to be the only instance in which anything except ligation of the parent artery has been attempted as a surgical measure. Subsequent bacteriological findings in the blood-clot of the aneurysm doubtless precluded any chance of final success from aneurysmorrhaphy in this particular patient, but in other aneurysms which have a non-infective cause the method can hardly yield results more disastrous than those attending ligation; the difficulties are by no means great, and the method is worth consideration by those who may be confronted with aneurysm of this blood vessel on laparotomy.

Clinical History of Case

A married woman aged 61 was admitted into Middlesex Hospital under my care on June 22, 1938. A history was obtained of two years' indigestion unrelieved by food; there were intermissions between the bouts of severe pain, but there had been continuous epigastric discomfort throughout the whole period. The last and final bout of pain had followed a wholesale dental extraction, and for a fortnight before the patient's admission to hospital there had been persistent severe melaena, punctuated by three sharp attacks of haematemesis, which had brought her haemoglobin at one time down to 30%. A continuous-drip blood transfusion had been employed on several occasions, and on her arrival at hospital her haemoglobin had risen again to 70%, and the red cells numbered 3.6 millions. For a week there was no pain or further haemorrhage; obvious melaena ceased, although the faeces still gave a very strongly positive benzidine and guaiacum reaction. The Wassermann reaction was negative.

On July 1, 1938, the patient was suddenly seized with most violent abdominal pain; she vomited blood and collapsed. A diagnosis of a perforated peptic ulcer and concomitant ulcer-haemorrhage was made, and the abdomen was opened under regional anaesthesia and intravenous skophedal; a blood transfusion was at once begun. No ulcer-perforation was found.

The liver, gall-bladder and pylorus were bound together into a pulsating mass; the gall-bladder was much distended and bluish in colour; the duodenum and small intestine contained much blood. The existence of an aneurysm in connexion with the hepatic arterial system was now discernible, but the precise nature of its origin and of any recent change in its condition was not at the moment apparent. A better exposure of the tumour was obtained by removal of the pyloric portion of the stomach and the careful separation of the distended gall-bladder from its hepatic bed, the organ being cautiously stripped downwards and mesially from fundus towards neck; this separation was facilitated by the injection of saline into the subserosa of the gall-bladder and between the wall of the latter and Glisson's capsule. The upper and lower boundaries of the pulsating tumour had now been defined and also mobilized.

The distended gall-bladder was next opened, and was ascertained to be filled with recent blood and also blood-clot; blood was indeed seen issuing into the gall-bladder cavity in a steady stream through a small opening on the mesial aspect of its wall. Bacteriological examination of the blood subsequently revealed the presence of streptococci and a scanty growth of *B. coli*. *Clostridia welchii* were not present in the gall-bladder contents.

The gall-bladder was now removed, with some recent soft clot on the anterior aspect of the pulsating tumour; a little laminated clot was also dissected away, some haemorrhage taking place the while from the opening in the aneurysm despite efforts to compress the hepatic arterial stem. A considerable "button" of aneurysmal wall was left on the artery and a reconstructive aneurysmorrhaphy was performed, the remains of the sac being sutured in layers. All haemorrhage having been arrested, the abdomen was closed without drainage. Next day the condition of the patient was satisfactory, with a pulse of 88; but she afterwards slowly sank and died 40 hours after operation. The post-mortem examination did not demonstrate any failure in operative technique as responsible for the patient's death.

Necropsy.—The lungs showed marked hypostatic congestion and in parts early bronchopneumonia. The pericardium contained 3 oz. of fluid. *Heart muscle* exhibited fatty fibrosis. The abdominal aorta and main arteries showed advanced atheroma; no evidence of syphilitic striation was observed. The kidneys were normal in size; the cortex was thinned, and there was patchy ischaemia, with obliteration of glomeruli. Histology: No changes indicative of a "transfusion kidney"; tubules in kidney rather dilated. Blood urea, 170 mg.; non-protein nitrogen, 125 mg. The spleen was packed with red blood cells. The liver showed toxic degeneration; portal vein and radicles were normal and healthy. The common bile duct

Diagram showing aneurysm of the hepatic artery which communicated with the gall-bladder.

was patent and healthy throughout its length. At the junction of the cystic artery and bifurcation of the hepatic artery, which was buried in a mass of laminated and more recent clot, there appeared a widening and a perforation of the arterial swelling.

The operation had not interfered with the patency of the arterial tree. The high blood urea and non-protein nitrogen suggested renal deficiency as at least a contributory cause of the fatal ending, and the fluid in the pericardium also supported this view. Nevertheless I have repeatedly stressed the disastrous results which attend operations for haematemesis from peptic ulcer undertaken after the first 36 hours; the necessity for operation was imposed upon me in this instance on account of a mistaken diagnosis of perforation. All these untoward circumstances combined to determine the fatal issue.