In America the Narcotic Drugs Acts and Regulations appear to have been framed on the assumption that addiction was a vice and not a disease. The restrictions as regards medical practitioners have been such that large numbers have refused to have anything whatever to do with drug addicts. The drug addict is often prevented from getting by legitimate means any supply of drug to tide him over a period preceding the commencement of a course of treatment, with the result that the illegitimate traffic of narcotic drugs has become most extensive.

CONCLUSIONS AS TO MORPHINE, HEROIN, AND COCAINE.

To sum up the present position with regard to morphine, heroin, and cocaine addiction in this country—

(1) Further research is needed on the pathology, symptomatology, and treatment of drug addiction.

(2) The regulations in force are necessary for the control of an evil which is a menace to the public health and well-being of the State, and which, if uncontrolled, would certainly seriously increase.

(3) The regulations in force are at present adequate as regards the legal restrictions imposed, and it is advisable that they should be interpreted with moderation and breadth of view as regards the difficult and imperfectly understood problem of drug addiction.

(4) Compulsory restraint for treatment of drug addicts is desirable, on purely medical grounds, but could not be generally enforced at present, owing to the lack of adequate State provision.

(5) The most effective method of carrying out the spirit of the regulations of the Dangerous Drugs Act is by the loyal co-operation of the professions concerned with the State authorities.

OTHER DRUGS OF ADDICTION.

The Veronal Group.—Barbitone or veronal, medinal, propional, dial, and luminal, are all dangerous from the liability to addiction. Their continued use leads to the development of a definite symptom-complex, such as an abnormal mental condition, in which delusions and visual hallucinations may occur. The speech may become thick and indistinct and visual disturbances may occur. The gait often becomes ataxic. The veronal habit leads to a disorganization of the moral sense. Veronal and its allies are all toxic and not free from danger where idiosyncrasy is present. There is a great danger of the development of addiction. A common sequel of veronal addiction is suicide, and I have seen a number of such cases. Usually a large dose is taken with the intention of suicide. In one case a young woman, who was the victim of the veronal habit, drank a large quantity of lysol with fatal result. None of the drugs in this group should be obtainable except on medical prescription. At present they are included in Part I of the Poisons Schedule and can be obtained by the public on signing the Poisons Register. I regard all the members of this group as most dangerous hypnotics and strongly advise their avoidance.

Cannabis Indica (Indian hemp) is in common use in Egypt and Eastern countries as a drug of addiction. Bhang or hashish is the name given to the preparation, consisting of the leaves, small stalks, and fruits. "Charrish" is the term applied to the preparation of the plant prepared for smoking. The drug produces pleasurable sensations and is a deliriant poison. A case of its sale in this country as "Persian opium" has recently occurred. Owing to its narcotic and addiction effects it would be desirable for the drug to be added to those included in the Dangerous Drugs Act.

Sulphonal and its homologues, trional and tetronal, are common hypnotics. They may give rise to addiction, and then suicide is not unlikely. It would be desirable that they should only be obtainable on medical prescription.

Paraldehyde may give rise to addiction. The symptoms of the condition are similar to those of alcohol and the treatment the same.

Ether may give rise to addiction, but is rarely met with in this respect at the present day.

Chloral also may give rise to addiction, but its use for such purpose is much rarer than formerly.

Chloroform addiction may arise from repeated inhalations. In one case seen by me a few years ago the patient, who was a scientific man of neuropathic type, inhaled the drug, with the object of killing the germs causing a chronic nasopharyngeal catarrh from which he suffered. The drug caused hepatitis and jaundice which ultimately proved fatal.

Dionin has only feeble powers in the causation of addiction, though a few isolated cases are recorded. It has been used in the treatment of morphine addiction, and is of some value in warding off withdrawal symptoms. It is not included amongst the dangerous drugs.

Codeine is not really dangerous as an addiction drug, and has been wisely excluded from those in the Dangerous Drugs Act.

CONCLUSION.

With regard to legislation relating to drug addiction, let us have confidence in those experienced administrators who have charge of this aspect of the question. Let us be temperate in our desires for new legislation, remembering that too hasty legislation may do more harm than good. It is only by the steady method of advance, each step having been carefully thought out and considered in all its aspects, that true progress will be made.

COCAINE AND ITS SUBSTITUTES.

BY

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PURELY as a local anaesthetic, cocaine is probably unsurpassed. Disadvantages are, however, associated with its use, especially its toxicity, the varying susceptibility of individuals to its toxic action, and its instability.

An endeavour has therefore been made to examine the evidence available from the clinical side on these points; and further, by experiment, to compare cocaine and some of its substitutes, particularly two recent introductions—*butyn* and *atoxodyne*.

The toxicity of cocaine appears to be less than is frequently asserted. The evidence as to "idiosyncrasy" is scanty; and, especially in the most interesting cases of reported death from small doses, the accounts are so meagre as to preclude any chance of criticism.

EVIDENCE OF REPORTED CASES.

The evidence of published cases was examined to discover if possible how far the alleged variable toxicity of cocaine is due to "idiosyncrasy" of the patients, and how far to varying methods of administration. Fifty fatal and very many more non-fatal accidents were investigated. The total available references in the medical libraries of Bristol University and the Royal Society of Medicine extend over a period of about forty years. In a number of cases it was found that reports have been copied from one journal to another several times, often with loss of accuracy.

Deaths Wrongly Ascribed to Cocaine.

Examination of the reports showed that of the fatal cases four seem to have been wrongly ascribed to cocaine poisoning.^{1,2} For example: (a) Dental injection, dose unknown; the patient became ill on the eighth day and died on the eleventh. Autopsy=septicaemia; coroner's verdict, "blood poisoning." No mention or evidence of poisoning by cocaine. (b) Abadie's patient, aged 71, received two-thirds of a grain subcutaneously. She was considered at the time to have died of apoplexy (second attack). Neither time nor mode of onset of symptoms, nor appearance after death, correspond with cocaine poisoning.

Dose of Cocaine Used in Fatal Cases.

The remaining cases include all those in which, though details are lacking, death was ascribed to cocaine poisoning. It is to be remembered that cocaine in the last century was used with a freedom and in a dose now uncommon. For example, one surgeon reports 1,600 operations in which injections up to 4 grains were given as a routine, with no serious accidents³; another frequently injected over 1 grain in children, but not under 3 years old⁴; a third had alarming accidents among infants between 3 and 6 months old, from spraying or swabbing the fauces with 4 per cent. solution⁵; a fourth

administered 5 grains daily for months in one case⁶; 8 grains and even 15 grains were advised for hydrocele operation, where of course part was recovered⁷; a textbook advises 2 drachms of 5 per cent. solution (5½ grains) for urethral injection.⁸ Fatal and even serious accidents from clinical use seem, however, from the available published reports to have been rare.

Oral Ingestion.

In 13 cases death was due to taking a large dose by the mouth.^{2 9 10 11 12} The dose was known in 8, average 22 mg. per kilo.* The smallest fatal doses were: (a) about 10 grains in 2 drachms, taken by a woman—it might have been more¹⁰; (b) 12 grains in 10 per cent. solution taken by a girl.¹¹ A man survived 9 grains solid¹³; and others 10 grains, 22 grains, and it is said 46 grains, diluted.¹⁴ One patient took at least 60 grains daily for months, but died when she took 30 grains in one dose.¹²

Subcutaneous Injection.

Six cases died after subcutaneous injection. In 5 a definite overdose was given—namely, 20, 19, 17, 12, and 8 grains respectively.² Injection of 4 grains into the breast caused death.¹⁵ Doses of 18, 15, and 14 grains (in 35 per cent. solution) were survived.¹⁷

Submucous Injection.

Twelve cases of death are reported following injections in adults for tonsil operations.²² In 4, owing to carelessness, strong solutions were injected instead of weak—for example, 20 per cent. instead of 0.2 per cent.; the victims received, therefore, one hundred times the intended dose. In 4 more the dose was not known. In the remaining cases the doses were (a) 3 drops of ½ per cent. solution (=1/50 grain); (b) ¼ grain; (c) 20 minims of 1 per cent. solution in adrenaline 1 in 1,000 (= 1/5 grain of cocaine); (d) 2 drachms of 0.2 per cent. solution in adrenaline 1 in 1,000 (=½ grain of cocaine). It seems hardly credible that the injected cocaine alone caused death in (a). In (c) and (d) the dose of adrenaline injected was too high for safety. In none of these cases is mention made of painting the fauces before injection; if this were done the cocaine absorbed may have largely exceeded the doses given; details of all are scanty. In each case death occurred almost at once, showing that the drugs reached the general circulation very rapidly. (It is noteworthy that injections for tonsil operations account for a number of fatal accidents with several anaesthetics, even dilute novocain; the painting before injection has perhaps received too little attention in some cases.) One death followed injection of 10 per cent. solution of cocaine into the nasal septum in mistake for 1 per cent.²²

Dental injections were twice fatal; dose unknown.^{1 19} Two grains and even less gave rise to trouble in a number of dental cases. Very many accidents occurred when dealing with acute inflammatory conditions: the vascularity present, and possibly injection under pressure, appear to have been factors. In one series all the serious accidents occurred with 10 per cent. or stronger solutions.²⁰

In one case 1½ grains injected for rectal fistula operation caused death in four minutes.¹⁶ Injections for haemorrhoids caused convulsions with 5 grains and 3 grains, and less serious trouble with several doses of this order.¹⁵

Injection into Cavities.²⁴

Death followed injection of 6 grains in 5 per cent. solution into a recent hydrocele. It was considered that "this relatively feeble dose," safe in chronic hydrocele, was in this case rapidly absorbed by the unthickened tunica vaginalis.

Injection into the recently wounded urethra was responsible for three deaths—doses, 3 grains,²² 2½ grains, and 1 grain.¹⁶ Death in each case occurred in a few minutes. Absorption, however, from the intact urethra is rapid^{30 36}—7 grains caused convulsions.²³

A dose of 22 grains injected into the rectum caused death in a few minutes.²⁴ (The surgeon committed suicide.)

Surface Absorption.

Application of 4 per cent. solution to abraded skin caused death in a few minutes; dose unknown.¹⁶ Four fatal accidents followed application to the fauces; doses unknown.^{2 22} In another case death followed the application of 20 per cent. solution to the larynx.²²

Numerous accidents, mainly not very serious, are reported in nose and throat work, especially with 10 per cent. or stronger solutions (without adrenaline). Fullerton in 1891 pointed out that absorption from the nasal mucosa was particularly rapid.²⁵ In this connexion it is worth remembering that the addict of one type, who spares neither pains nor ingenuity, has discovered that application of solid cocaine to the nasal mucosa is the most rapid, efficient, and economical method of introducing a toxic dose into his cerebral circulation.

* 1 mg. per kilo = 1 grain for the average adult man.

SUMMARY.

Summarizing the above brief survey of 50 reported fatal cases of cocaine poisoning:

Death was not due to cocaine in	...	...	...	4
Death followed oral ingestion in	...	...	...	13
Death followed overdose in	...	...	...	12
Dose was unknown in	...	...	...	12
Death followed employment of a dose stated to be under 5 grains in	...	...	...	9
				50

In the last class, in one case 4 grains was injected into the breast. In the remaining 8 death occurred in a few minutes—clear evidence that the drug had very rapidly entered the general circulation. This appears to be the essential factor in all these cases.^{34 35} The circumstances of each case so far as they are known have been briefly considered.

CLINICAL DOSES.

Judging from the published reports we may infer:

A. Fatal poisoning from clinical doses of cocaine is rare. "Idiosyncrasy" to cocaine in this sense is not established.

B. The lethal dose of cocaine for man by subcutaneous injection or by the mouth appears to lie between 12 mg. and 25 mg. per kilo, depending on the concentration.³⁷

C. The same dose of cocaine in strong solution is much more dangerous than in weak.

D. For ordinary subcutaneous injections in dilute solution (1/4 per cent.), especially with adrenaline, the old "maximum dose" of 3 grains should be safe.

E. In vascular, including acutely inflamed, tissues, and other situations where the drug may rapidly enter the circulation, very great caution is necessary. This may apply particularly to injections for tonsil operations. (The intravenous lethal dose of cocaine for man has been estimated at about 1.5 mg. per kilo.²⁶ Cocaine has, however, been used intravenously.)

Other points which appear especially from the study of non-fatal cases (to which it has not been practicable to advert in this paper) are:

F. Absorption from mucous surfaces is often rapid.

G. Accidents have become much less common since adrenaline has been in use. (Injection, however, of strong adrenaline into vascular tissue is itself a source of danger. Recent authorities advise 1 in 100,000 solution for injection, 1 in 10,000 solution for mucous surfaces.²⁷)

DEATHS FROM COCAINE SUBSTITUTES.

It must be remembered that occasional severe and even fatal accidents have occurred with all the cocaine substitutes that have been extensively used.²⁶ The preliminary report of the American Committee on Toxicity of Local Anaesthetics contains a table of recent fatal cases³³:

	Deaths.
Stovaine	1
Alypin	1
Novocain	3
Novocain and cocaine	10 (a)
Apothesin	4
Butyn	4 (d)
Butyn and cocaine	1 (b) (d)
Cocaine	18 (c)
	42 deaths

(a) Presumably injection of novocain after painting with cocaine.

(b) Injection of butyn after painting with cocaine.

(c) Fifteen of these included and analysed above.

(d) See below, "Butyn."

This table possibly bears some relation to the frequency of use of the different drugs.

STABILITY OF COCAINE.

Cocaine base in solution is said to be very unstable. The hydrochloride in moderately strong solution is stable, unless it becomes alkaline. A specimen, containing 1/2 per cent. salicylic acid, was found, after two years in a stock bottle, to be of the same anaesthetic power and toxicity as a fresh specimen. This same solution, although doses had been frequently taken from the bottle without precautions, was sterile.²⁸ Cocaine hydrochloride can be sterilized by boiling;

it is not damaged by short boiling in the absence of alkali. (N.B.—Some glass is alkaline.³¹)

De Havilland Hall pointed out in 1888 that alkali increased the efficiency of cocaine.²⁹ Recent experimental work shows that on mucous surfaces the anaesthetic power is doubled, the toxicity remaining unaltered, by alkalinization.³⁰ This does not apply to injected cocaine. The solution must be prepared at the time of use.

EXPERIMENTAL COMPARISON OF LOCAL ANAESTHETICS.

Experiments are being made in the Pathological Laboratory of Bristol University* on rabbits, guinea-pigs, and mice, with cocaine, novocain, stovaine, alypin, butyn, and atoxodyne.

The particular questions, among others, to which an answer is sought, are:

A. To what extent does the safety of these anaesthetics vary with (1) concentration of drug; (2) manner of administration; (3) presence of adrenaline?

B. Why do experimental and clinical estimates of comparative toxicity of various local anaesthetics differ?

C. Has the answer to B a bearing on the application of experimental results to clinical work?

D. What is the experimental toxicity of butyn and of atoxodyne?

These notes indicate briefly the results so far obtained; experimental investigation is proceeding.

Comparative Toxicity.

Comparative toxicity was estimated by a determination of the lethal dose by subcutaneous injection. As an example, the following abridged protocol is given:

No. 50.—Rabbit, 1.95 kilos; injection of 0.95 c.c.m. of 20 per cent. solution of alypin = 190 mg. = 98 mg. per kilo.

Time (minutes).

5 Weakness of limbs, coarse twitching.

9 Urgent dyspnoea, pupils dilate.

11 Lying on side, weak convulsion.

44 Flaccid paralysis.

72 Apparently moribund.

98 Condition improving.

Later the animal was quite normal.

Result: Severe toxicity; recovery.

Minimal Lethal Dose.

From a series of such results the minimal lethal dose for the drug by subcutaneous injection at a given concentration, for each species, was determined. Thus, for example, the toxicity of cocaine in guinea-pig (subcutaneous 5 per cent. solution) was as follows:

No.	Dose in mg. per kilo.	Result.
59	30	Severe toxicity; recovery.
60	35	Severe toxicity; recovery.
64	40	Very severe toxicity; recovery.
65	45	Death in ten minutes.
58	50	Death in eight minutes.

Therefore the M.L.D. = 45 mg. per kilo.

Having thus determined the M.L.D. for each animal, with each drug, using the same concentration of each drug with any given species, a comparison of their experimental toxicities can be made and expressed as a fraction of the toxicity of one, say cocaine, taken as the standard. Of course, the higher the M.L.D. the lower must be the toxicity.

Comparative Experimental Subcutaneous Toxicities.⁴²

	Mouse.	Rabbit.	Guinea-pig.
Cocaine	1	1	1
	[M.L.D. = 80]	100	45]
Novocain	1/8	1/8	1/11
Stovaine	1/9	1/5	1/3
Alypin	3/4	1	2/3
Butyn	2	1 1/2	3/4
Atoxodyne	1/10		1/12

Concentration.

The effect of concentration was investigated—for example, cocaine given subcutaneously to rabbits.

20 per cent. solution	M.L.D. = 100 mg. per kilo.
4 per cent. solution	M.L.D. = 110 mg. per kilo.

A further variation when these limits are exceeded, and a similar result with novocain and alypin, is indicated by experiments not yet complete. Butyn does not appear so much influenced in its effects by concentration of the injected solution.

* For this my thanks are due to Professor I. Walker Hall.

Inasmuch as a large amount of experimental work has been done with concentrations of drugs greatly exceeding those used clinically, unless the effect is approximately the same with all drugs an allowance must be made for this.

Influence of Adrenaline.

The influence of adrenaline was investigated by injecting a hyper-minimal lethal dose of anaesthetic; and at the same time adrenaline of a strength of 1 in 5,000 (a) together, (b) in separate sites. For example:

No. 75.—Rabbit, 2.54 kilos. Injection of 7 c.c.m. of 4 per cent. solution of cocaine hydrochloride containing 1.1 mg. adrenaline. Dose of cocaine = 110 mg. per kilo. Result: Severe toxicity; recovery.

No. 79.—Rabbit, 1.95 kilos. Injection in two sites of 4.30 c.c.m. of 1 in 5,000 adrenaline and 5.40 c.c.m. of 4 per cent. solution of cocaine hydrochloride. Dose of cocaine = 110 mg. per kilo. Result: Death in nine minutes.

From these experiments one may deduce that the presence of 1 in 5,000 adrenaline lowers the toxicity of subcutaneous cocaine. With strong solutions of anaesthetic the effect is not well shown. Other anaesthetics are being investigated.

Toxicity by Surface Absorption (Nasal Mucosa).

The effect of applying these anaesthetics to the nasal mucous membrane was examined by gently smearing hypolethal doses on the nasal passages of rabbits. It is possible that some of the solution was swallowed. Only one nostril could be used, or the drug got blown out; the nostril investigated was closed with a finger. The results of some experiments can be tabulated thus:

Drug.	Dose given by Nostril (mg. p.r. kilo).	M.L.D. subcutaneous (mg. per kilo).	Result.
Cocaine	90	100	Death in three minutes.
Cocaine and adrenaline	90	100	Death in fourteen minutes.
Alypin	60	110	Death in six minutes.
Butyn	70	60	Severe toxicity; recovery.

In these experiments strong solutions were used, and it is probable that the factor of relative solubility has a large place in the results. At least, however, with cocaine and alypin strong solutions applied to the nasal mucosa of rabbits appear not less toxic than subcutaneous injections.

Clinical Toxicity.

The clinician estimates toxicity by the dose that exposes his patient to risks of serious central nervous disturbances—for example, syncope, dyspnoea, etc. Such a dose is less than the lethal dose, but with each species, each anaesthetic, possibly each variation in concentration, this dose, which we may call the "maximum clinical dose," may be a different fraction of the M.L.D. Let us call this fraction the danger ratio. Dixon⁴¹ investigated the toxicities of cocaine in animals, using convulsions as his standard: he found a series of values quite unlike those from M.L.D. But, although in man syncope, etc., is produced by a smaller dose than are convulsions, we may use the latter phenomena as an indication in animals of the effects produced by hypolethal doses. Working on these lines we find that the "danger ratio" with different anaesthetics is:

Cocaine	Small.
Novocain	Moderate.
Alypin	Moderate.
Butyn	Large.

That is to say, a small fraction of the lethal dose of cocaine may produce syncope, while a larger fraction of the lethal dose of butyn is required.

Idiosyncrasy.

The "maximum clinical dose" of cocaine appears to be about 1/8 M.L.D.—that is, about 3 grains for an average adult man.* It is perhaps because of this low value of its danger ratio (1/8) that cocaine has been attacked on the ground of idiosyncrasy. Many clinicians, habitual users of cocaine, have worked with injections of about this dose. Possibly for the same reason reported cases of fatal poisoning from the clinical use of cocaine are rare.

* By injection.

Application of Experimental Results.

If the thesis as to danger ratio is established, when we wish to apply our animal experiments in the clinic it seems clear that we must know approximately what is the ratio for a given drug with the higher mammals. Further, an anaesthetic with a low danger ratio is much safer for trial than one with a high, the risk of incautiously approaching the lethal dose being less.

Butyn.³⁸

Experimentally butyn appears, in the hands of four independent workers, to be of toxicity equal to cocaine or rather more toxic. Many of the experiments were done with strong solutions, and there seems some evidence that with weak solutions the toxicity of butyn is less reduced than that of cocaine—that is, its relative toxicity is greater. It is said to have special advantages in eye work.³⁹ In the nose it seems an effective anaesthetic, but more irritant than cocaine.⁴⁰ By courtesy of the proprietors I have received notes of five deaths following its clinical applications: two for septal resection—5 per cent. solution on tampon; two for tonsil operation*—1/4 per cent. solution injected—no evidence of overdose; one case of definite overdose. Obviously considerable caution is required in using it.

Note on Atoxodine.

The claim of this anaesthetic to be without toxicity was found to have no foundation: the toxicity is low. It appears useless on mucous surfaces.

Summary.

1. The toxicity of various local anaesthetics was compared experimentally by determining the minimal lethal doses.
2. The effect of dilution was found to be a lowering of toxicity.
3. Addition of adrenaline definitely lowered toxicity.
4. It appears that the dose of anaesthetic which will produce alarming symptoms is with different drugs a different fraction of the M.L.D., cocaine having a small fraction, for example, butyn a larger.
5. Caution is required in using butyn.

REFERENCES.

[Few references to the non-fatal cases have been included. It has not been practicable to verify the references marked *.]

- * British Association Report, 1913, p. 238.
- Richardière, quoted by Reclus, *Bull. Soc. de Chir.*, 1891, p. 766.
- Reclus, *Bull. Soc. de Chir.*, 1891, p. 755.
- Félizet, *Ibid.*, p. 790.
- Holt, quoted by Mattison, *Therap. Gaz.*, 1888, p. 16.
- Hammond, quoted by Dunn, *Ibid.*, p. 515.
- Tillaux, *Bull. Soc. de Chir.*, 1891, p. 763; Baillet, *Thèse de Paris*, quoted by Berger, *Ibid.*, p. 751.
- * Caird and Cathcart, *A Surgical Handbook*.
- * Montali, *Lo Sperimentale*, 1888; Mattison, *Therap. Gaz.*, 1888, p. 16; Garland, *Lancet*, 1895, ii, p. 1104; Inquest case, *Ibid.*, 1889, i, p. 292; Bose, *BRITISH MEDICAL JOURNAL*, 1913, i, p. 16.
- Curgenven, *Quart. Med. Journ. Sheffield*, 1895-96, p. 152.
- Johnston, *BRITISH MEDICAL JOURNAL*, 1895, ii, p. 1162.
- Knight, *Quart. Med. Journ. Sheffield*, 1899-1900, p. 307.
- Walker, *Lancet*, 1895, i, p. 261.
- v. Ploss, *Therap. Gaz.*, 1888, p. 373; Palmer, *Lancet*, 1898, i, p. 718; Mann and Brend, *Toxicology*, 1922, p. 511.
- * Zambianchi, *Gazz. degli Ospedali*, 1888.
- * Mattison, *Dublin Journ. Med. Science*, 1895, i, p. 116.
- * Hammond, quoted by Mattison, *Ibid.*; Championnière, *Bull. Soc. de Chir.*, 1891, p. 770; Barratt, *BRITISH MEDICAL JOURNAL*, 1896, i, p. 1032.
- Earle, quoted by Mattison, *Therap. Gaz.*, 1888, p. 16.
- Labbé, *Bull. Soc. de Chir.*, 1891, p. 757.
- Lepine, quoted by Reclus, *Ibid.*, p. 769.
- Berger, *Ibid.*, p. 765.
- Tivy, *BRITISH MEDICAL JOURNAL*, 1905, ii, p. 868.
- Call, quoted by Mattison, *Therap. Gaz.*, 1888, p. 16.
- Vinogradoff, *Lancet*, 1889, ii, p. 656.
- Fullerton, *Ibid.*, 1891, ii, p. 63.
- Sollmann, *Manual of Pharmacology*, 1922, p. 296 et seq.
- Labat, *Regional Anesthesia*, 1923; Canuvt and Rozier, *L'Anesthésie locale*, 1920.
- * Author's experiment; cf. also Ref. 10 above.
- Lancet*, May, 1888.
- Sollmann, *Journ. of Pharmacol.*, 1918, vol. ix, p. 1.
- Holbrook, *Journ. Amer. Med. Assoc.*, 1912, p. 721; Mills, *Journ. Pharmacol.*, 1920, vol. xiv, p. 355.
- Mayer, *Journ. Amer. Med. Assoc.*, 1920, p. 315.
- Mayer, *Ibid.*, 1923, p. 947.
- Eggleston and Hatcher, *Journ. Pharmacol.*, xiii, 1919, p. 433.
- Schaps, *Deut. Zeit. f. Klin.*, 1920, 155, 1.
- Macht, *Journ. Pharmacol.*, xvi, 1921, p. 435.
- * Cf. Zantchevski, *St. Petersburg Inaug. Dissert.*, 1888; see also Ref. 28 above.
- Bulson, *Journ. Amer. Med. Assoc.*, 1922, p. 343.
- Beaumont, *BRITISH MEDICAL JOURNAL*, January, 1923, p. 57.
- * Cf. Hill, *Ibid.*, 1923, ii, p. 876.
- Dixon, *Manual of Pharmacology*, 1921.
- * Cf. Le Brecq, *BRITISH MEDICAL JOURNAL*, 1909, vol. i.

* Cocaine was painted on fauces in one case.

A British Medical Association Lecture

ON

THE PATHOLOGY OF GASTRIC ULCER.

DELIVERED TO THE DERBY DIVISION, MAY 18TH, 1923,

BY

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(Continued from page 957.)

PART II.—PATHOLOGICAL OBSERVATIONS ON GASTRIC AND DUODENAL ULCER.

THE statistical data utilized in this section were obtained from two sources: (a) a consecutive series of 6,800 autopsies at the Leeds General Infirmary, of which a special group of 1,500 were intensively studied from the point of view of gastro-duodenal pathology, and (b) a series of 120 stomach specimens removed at operation and submitted to microscopic examination.

A. INCIDENCE OF PEPTIC ULCER.

In the intensively studied series of 1,500 autopsies there were 130 cases of gastro-duodenal ulceration (that is, 8.7 per cent.) equally distributed between the two organs (4.5 per cent. in each). In 28 cases (1.9 per cent.) chronic gastric ulcers were present, and in 58 (3.9 per cent.) chronic duodenal. In the full series of 6,800 autopsies there were 150 cases with chronic gastric ulcer (2.2 per cent.) and 200 with chronic duodenal ulcer (2.9 per cent.). The relative frequency here shown (3:4) differs considerably from that revealed by clinical statistics. Sir Berkeley Moynihan's (1923)²³ latest review of 718 cases coming to operation shows duodenal ulcer to be three times more frequent than gastric, while in the Mayo Clinic figures (C. H. Mayo, 1920)²⁹ for 5,723 cases the ratio is practically 4:1. This discrepancy between autopsy and clinical statistics may be due to the surgeon seeing a relatively larger proportion of duodenal ulcer cases, which would suggest that, symptomatically, this is the more severe disease, or it may be due to the fact that gastric ulcer is the more difficult to diagnose, with the result that fewer cases come to operation. On the other hand, the partiality may lie with the autopsy figures. Gastric ulcer is the more serious and more fatal disease, with a much heavier operation mortality; a larger proportion of the duodenal cases, therefore, will recover.

The scars of healed ulcers are met with fairly frequently. In the series of 1,500 autopsies, 42 cases (2.8 per cent.) showed gastric scars, and 36 cases (2.4 per cent.) duodenal. Coincident chronic lesions (ulcers or scars) of the stomach and duodenum were met with in 7 cases, or 0.45 per cent. of the whole, but in only a single instance did an open chronic ulcer coexist in the two organs.

B. AGE AND SEX INCIDENCE.

Acute ulcer of the stomach and duodenum occurs with a fairly uniform frequency throughout the decades, except that it is rather less common under 20. Chronic ulcer is rare under 20, only 1.5 per cent. of all cases coming to autopsy in the first two decades. In the present series 90 per cent. of cases of chronic gastric ulcer came to autopsy between the ages of 30 and 69, while the corresponding figures for chronic duodenal ulcer and cancer of the stomach were 84 per cent. and 96 per cent. respectively.

The older statistical tables (Bolton, 1913¹) show for the most part the heaviest incidence of gastric ulcer (acute and chronic) between the ages of 20 and 40. In this series the highest figures are found between the ages of 40 and 60—namely, 42 per cent. of all acute ulcers and 56 per cent. of chronic.

Chronic gastric ulcer shows a slight difference in the age incidence in the two sexes, being met with rather later in life in males. This is well shown by the fact that, whereas in females only 7.5 per cent. of ulcers occur at age 60 or over, in males the proportion in these later decades is 23.5 per cent. In both sexes the heaviest incidence is in the fifth and sixth decades—52 per cent. in males, 62 per cent. in females.