no casts. The blood urea was 26 mg. per 100 c.cm., and the urea concentration was 1.95 per cent. Cultures from faeces yielded colonies of *S. viridans* only: 1 c.cm. of a first subculture of the living organism was injected into the veins of a rabbit; the urine collected and tested three weeks later was normal. Microscopical examination of the kidneys showed nothing pathological.

The girl (No. 13) had a history of haematuria, commencing three weeks after birth. Her systolic blood pressure was 118 mm. Hg, diastolic 75 mm. Hg. The heart was not enlarged, there were no bruits, and the arteries were normal. There was only a trace of albumin in the urine, which was faintly positive to chemical tests for blood. Microscopically a few red corpuscles, some uric acid crystals, and one hyaline cast were seen. The blood urea was 17 mg. per 100 c.cm.; urea concentration test 2.1 per cent. Culture from faeces yielded numerous *S. viridans*, and a few colonies of a haemolytic streptococcus appeared on the plate; 1 c.cm. of a living subculture of the above was injected into the veins of a rabbit and the urine collected and examined three weeks later. It showed a faint trace of albumin on boiling, and microscopically a few red corpuscles, numerous pus cells, but no definite casts. Culture of a fresh specimen of the urine failed to produce any streptococcal colonies. The rabbit was then killed by chloroform, and the kidneys examined by Dr. Newcombe, who reported as follows: "Glomeruli rather swollen and some of them contain a small amount of albuminous exudate. No sign of leucocytic infiltration. Tubules show some early fatty degeneration."

The small dose of streptococci given, and the shortness of time intervening between the injections and the microscopical examinations, may account for the relatively slight changes found in the kidneys.

Other cases of nephritis occurring in a family may be of interest.

At the beginning of May, 1924, two brothers, Charles J., aged 17, and Harry J., aged 14, were admitted to the Medical Unit wards of St. Mary's Hospital suffering from general oedema, blood and albumin in the urine, and an increase of blood pressure. They had been delivering milk early one morning; both got wet through and cold, both developed symptoms of nephritis, and they were admitted on the same day. There was no evidence of any infection immediately preceding the onset in either case. They both had scarlet fever five years before admission, and the elder brother had had measles, diphtheria, and chicken-pox as well. There was no history of oedema or albuminuria following these attacks.

The mother states that her father, an uncle, and her grandmother died of cancer, while her grandfather, two uncles, and an aunt died of consumption. There was, however, no family history of kidney disease. The elder boy proved to be a case of acute nephritis. On admission his renal efficiency was impaired—blood urea 0.056 per cent.; urea concentration test 1.6 per cent. After treatment the blood urea fell to 0.041 per cent.; urea concentration test 2.75 per cent. of urea. He has been discharged, and has been in the best of health ever since.

The condition of the younger boy on admission was more severe. He had considerable oedema, with albumin, blood, and casts in the urine. The apex beat was in the mid-clavicular line, but there was no bruit. The systolic blood pressure was 160, diastolic 100. The fundi were normal. Blood urea 0.146 per cent., urea concentration 1.7 per cent. The picture was one of chronic parenchymatous nephritis with considerable interstitial changes, progressing towards small white kidney. He was discharged relieved some weeks later.

On readmission in October, 1924, his condition had deteriorated considerably. Oedema, drowsiness, headache, and nausea were marked features. The breath smelt urinous. The apex beat was $1\frac{1}{2}$ inches to the left of the mid-clavicular line, extra-systoles were present, but no bruits. The urine was scanty, and contained 0.8 per cent. albumin, granular and hyaline casts, but no blood. Urea concentration 1.35 per cent., blood urea 0.240 per cent. In the end he developed pericarditis and died on February 16th, 1925. Post mortem small white kidney was found.

COMMENTS.

1. Hereditary familial or congenital nephritis is a definite entity, and the kidneys in these patients are more susceptible to damage by the toxin of an unknown organism than is the case in the normal person.

2. The organism probably belongs to the streptococcal group.

3. In the first case investigated (No. 16) the coagulation time of the blood was delayed; intravenous injections of 1 grain of calcium chloride reduced the coagulation time and caused a reduction in the amount of blood and albumin in the urine. Calcium lactate given by the mouth is useless, as it is not absorbed by the intestines.

4. Cultures of *Streptococcus viridans* found in the stools of this patient, and of his cousin (No. 12), failed to produce the disease when introduced into the veins of a rabbit. Cultures of the stools of another case (No. 13), which showed both *S. viridans* and haemolytic streptococci, caused changes in the urine and kidneys of a rabbit after intravenous injections.

5. Deafness is a marked feature in nearly all these cases.

6. The male members of a family tend to develop nephritis and deafness and do not as a rule survive. The females have deafness and haematuria and live to old age.

7. The last couple of cases are interesting evidence of the variations in the course of nephritis. The kidneys of two members of the same family were attacked, apparently by the same organism, at the same time, and under exactly the same conditions. The elder brother contracted acute nephritis, which cleared up completely, the younger developed parenchymatous nephritis, passing into small white kidney, and ending in death.

I am indebted to Professor Langmead of the Medical Unit, St. Mary's Hospital, for leave to publish the notes on the last two cases.

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THE SCHICK TEST:

ITS APPLICATION IN AN INSTITUTION FOR MENTAL DEFECTIVES.

BY

ROBERT MUNRO, M.B., CH.B. ABERD.,
ASSISTANT MEDICAL SUPERINTENDENT, ROYAL EASTERN COUNTIES
INSTITUTION, COLCHESTER.

THE intradermal reaction in guinea-pigs was first used by Romer in 1907 for carrying out virulence tests in diphtheria. His technique was supplemented in 1913 by Schick, who introduced a test known by his name. It is possible by means of this test to determine whether or not an individual is susceptible to an attack of diphtheria. I have carried it out by injecting into the substance of the skin 0.2 c.cm. of standardized diphtheria toxin into the left arm. The most favourable site is the flexor aspect. The best results are obtained by using an "Aglä" all-glass syringe (Burroughs Wellcome) fitted with a No. 214 rustless needle. The needle is inserted intracutaneously for a distance of an eighth of an inch. If the injection has been accurately effected considerable force is necessary to move the plunger onwards. After the injection has been done a wheal about half an inch in diameter is visible which is caused by the pitting of the hair follicles. A corresponding dose of heated toxin is injected into the opposite forearm. A separate syringe is used for this control dose.

Four types of reaction may be observed, and in 90 per cent. of cases in healthy subjects the results may be read after twenty-four hours, though after thirty-six to forty-eight hours the reactions are clearer.

1. *Negative*.—After twenty-four hours both arms show no local reaction except a puncture where the needle was inserted. There may be slight transient redness due to trauma. This coloration fades in the course of twelve to twenty-four hours.

2. *Positive*.—At the end of twenty-four hours there is seen at the site of the injection a circumscribed area of redness which varies from a quarter of an inch to one inch in diameter. It attains its maximum intensity by the fourth day, and thereafter gradually fades, leaving a brownish pigmentation. Persons who show this reaction are susceptible to diphtheria if exposed to infection.

3. *Negative and Pseudo-reaction*.—There is a red flush with a dark centre; the characteristic is that the area of redness is equal or approximately equal on both forearms. The patient who shows this reaction is immune to diphtheria if exposed to infection. It is due to some unknown constituent in the toxin broth.

4. *Positive and Pseudo-reaction*.—In this case a pseudo-reaction is observed in addition to the positive reaction. A red flush appears on both arms. The flush, which is much larger on the test arm than on the control, lasts for a longer time. The reading of this arm is best seen on the fourth to sixth day. The reaction is rather rare.

The patient is immune if the reaction is negative or pseudo-negative, but is susceptible if the reaction is positive or pseudo-positive. It is advisable to examine the sites of the injection daily for five days, and it is very important that careful "readings" should be done, especially on the second and fourth days.

It is advisable to use the diluted toxin for the tests as soon as it is received from the laboratory, as otherwise it is liable to lose its potency, and should a dozen successive healthy adults give a negative result, provided the test has been carefully and properly applied, the conclusion should be that the toxin may not be absolutely reliable. The undiluted toxin is less expensive than the diluted; and it remains sterile and reliable for several weeks, provided reasonable care is taken in storing it.

Individuals who prove susceptible to diphtheria, as determined by the Schick test, may be rendered immune by the injection of toxin-antitoxin. The injection of diphtheria prophylactic causes immunity to develop a few weeks later, and this immunity may probably last during life. Diphtheria prophylactic consists of diphtheria toxin and diphtheria antitoxin prepared according to the standard adopted by the American Government. Babies up to 6 months old seem to be immune, and do not need immunization. The large majority of children between the ages of 6 months and 5 years give a positive reaction, and therefore it is possible to dispense with the Schick test between these ages. All these children may safely be injected with the toxin-antitoxin mixture without any preliminary testing. Between these ages it would seem advisable, as a routine measure, to immunize all children against diphtheria. It will be found that if children between the ages of 6 months and 5 years are tested the percentage of positive reactions will be about 60 to 70. Above the age of 5 years only those patients who exhibit a positive Schick reaction should receive the injections.

Active artificial antidiphtheria immunization is carried out by the injection of toxin-antitoxin mixture. It is usual to give three doses of 1 c.cm. subcutaneously at intervals of seven days. It may be considered preferable to begin with a smaller dose—for example, 0.2 c.cm.—and to follow it up with 0.4 c.cm., 0.8 c.cm., and 1.5 c.cm. at intervals of five to seven days. This is advisable in the case of those who give a positive and pseudo-reaction. The toxin-antitoxin mixture remains quite potent for several months if kept in a cool place.

The injections of toxin-antitoxin are attended by a certain amount of danger, and several unfortunate incidents have occurred. In an institution near Vienna forty children recently received prophylactic injections against diphtheria, and six died with symptoms of general diphtheria intoxication. Several of the others exhibited skin necroses of varying degrees. The fatalities were possibly due to a dissociation of the toxin-antitoxin mixture. As a result of several unfortunate occurrences an important modification has been described by Glennie in which the toxin is rendered non-toxic by the agency of formaldehyde. The resulting toxoid-antitoxin mixture acts as a very quick, reliable, and safe immunizing agent, and is generally free from unpleasant effects. Ramon has employed formalized toxin for conferring immunity on Schick-positive cases. He gives three injections, with an interval of three weeks between the first and second injections, and two weeks between the second and third injections. The doses employed are 0.5 c.cm., 1 c.cm., and 1.5 c.cm. He claims that by this method he is able to render 98 per cent. of his subjects immune in eight weeks. Certain observers have prepared a mixture of antitoxin and anatoxin. The resulting preparation has been called "ananti." It is a protein-free vaccine against diphtheria, and the time required to secure immunity would appear to be about the same as that taken by toxin-antitoxin. It does not seem advisable to attempt to confer immunity by toxin-antitoxin injections on patients who suffer from advanced heart and kidney affections, or in those recovering from acute infectious diseases.

Many adults after receiving the first dose of 1 c.cm. of toxin-antitoxin do not suffer from any local or general disturbance, except perhaps slight lassitude, and soreness of the arm at the site of the injection. In many cases it

is advisable to give a commencing dose of 0.5 c.cm., and follow up with two doses of 1 c.cm. at seven-day intervals. Patients who suffer from asthma, migraine, and debility should receive a small initial dose of 0.05 c.cm., and then 0.5 c.cm., followed by two doses of 1 c.cm. The frequency of local and general reactions increases with age. Severe reactions are rare before the age of 8 years.

The Schick test and antidiphtheria immunization were resorted to at the Royal Eastern Counties Institution, Colchester, because repeated small outbreaks of diphtheria had occurred during the last few years; twenty cases in fifteen apparently separate outbreaks occurred during 1924, and seventeen patients were attacked in the early part of 1925.

The test was commenced in 1925, and was applied only to patients whose relations or friends gave consent. The total number of patients tested was 1,037. The results were as follows:

Age.	Number Tested.	Positive.	Percentage of Positive Reactions.
Under 5 years ...	7	3	42.8
5 to under 10 years ...	48	16	33.0
10 to under 15 years ...	157	42	26.7
Over 15 years ...	825	187	22.6
Total ...	1037	248	23.9

The number of patients tested below the age of 5 years is too small to be of any practical value. It has been noted that between the ages of 2 and 5 there is a distinct loss of immunity, which increases again in children of school age. The latter increase is possibly due to these children acquiring from their neighbours slight infections, not sufficient to cause disease, but nevertheless allowing them to acquire the necessary antitoxin to combat infection. Interesting observations have been made which show that children who prove to be susceptible to diphtheria on admission to hospitals may gradually develop resistance to the disease. The longer the residence of these patients in hospitals the more likely is this immunity to result. It would appear that in diphtheria, to which our susceptibility is not very high, a spontaneous process of immunization can eventually occur by the inhalation of small and subinfective doses of bacteria.

It will readily be understood that in certain cases it is rather difficult to apply the Schick test accurately to mental defectives. Great care must also be exercised during the administration of the toxin-antitoxin mixture.

The number of members of the staff tested was forty-seven, and eighteen of these gave a positive reaction. This percentage (38 per cent.) is high, but may to a large extent be accounted for by the fact that the members of the staff who were subjected to the test, and encouraged to have it done, were those who were readily liable to sore throats, tonsillitis, and general minor maladies. The usual proportion of positive cases over the age of 20 with the Schick test is from 15 to 20 per cent.

I injected the 248 patients who gave positive reactions with toxin-antitoxin mixture obtained from Messrs. Burroughs Wellcome and Co., London. Calcium lactate was administered before and after the injections. The patients were then kept in bed for eighteen to twenty-four hours, the temperature taken, and the general condition carefully noted. Only one reaction occurred, and it was transient. It consisted of pyrexia, headache, and slight local reaction resulting from the injection of 1 c.cm. of toxin-antitoxin mixture; eighteen members of the staff also received the "injections." Unfortunately two mild reactions occurred which necessitated their confinement to bed for a few days. The initial dose employed was 0.5 c.cm., followed by two doses of 1 c.cm. The interval between the injections was seven days.

No case of diphtheria has occurred in the institution since the test was commenced and artificial antidiphtheria immunization carried out. I hope later to test the Schick-positive cases again, and, if necessary, to re-inoculate.

This may readily be effected from three to six months after the injections. It is claimed that after three injections with toxin-antitoxin 70 to 90 per cent. of those treated are found to be immune after eight weeks.

Interesting figures have been published showing that in America of 90,000 Schick-tested, immunized, and treated school children, 14 got diphtheria, while of a similar number not tested or treated 56 acquired the disease. An extensive campaign has recently been started in New York to popularize antidiphtheria immunization. It would seem advisable to apply the system whenever a careful study of the epidemiological situation convinces us that it may be resorted to with advantage.

Another application of the Schick test is in the clinical diagnosis of diphtheria. A true case of faucial diphtheria will give a positive Schick reaction, but a carrier of virulent diphtheria bacilli will give a negative reaction. One observer recently noted twelve cases of diphtheria in children with a negative Schick reaction, but in the majority of the patients the disease proved to be nasal diphtheria. The test is of the greatest value in school epidemics. Children can be tested, and within twenty-four hours may be divided into two groups—the immune and the susceptible.

One of the chief difficulties in the use of the Schick test is the pseudo-reaction, which is due to the presence in the toxic filtrates of some substance which is more stable than the specific one, and which causes rise of temperature and other reactions. It is important that the toxin-antitoxin mixture should not be used after exposure to a temperature below 0° C.

The most favourable age for the administration of diphtheria prophylactic is from 1 to 5 years.

I am much indebted to Dr. F. Douglas Turner, medical superintendent of the Royal Eastern Counties Institution, Colchester, for allowing me to publish this article and for his valuable advice regarding the work. My thanks are due also to Dr. R. A. O'Brien, director of the Wellcome Research Laboratories, for giving me suggestions in the necessary technique.

THE MORTALITY OF ACUTE APPENDICITIS.

BY

JOHN B. HUNTER, M.Ch., F.R.C.S.,

SURGEON, ROYAL NORTHERN HOSPITAL; LATE SURGICAL REGISTRAR,
UNIVERSITY COLLEGE HOSPITAL.

I PUBLISH the following figures in the belief that they indicate that the safest plan to adopt in treating acute appendicitis is to operate at once irrespective of the duration of the disease and of the local conditions obtaining.

All authorities are agreed that there is a steady increase in the incidence of appendicitis.

Deaths from Appendicitis in England and Wales (Registrar-General).

	Male.	Female.	Total.
1915	1441	1062	2503
1916	1474	1129	2603
1917	1390	1053	2443
1918	1298	1118	2316
1919	1278	1151	2429
1920	1389	1142	2531
1921	1474	1237	2711
1922	1524	1211	2735
1923	1608	1218	2826
1924	1545	1211	2756
1925	1624	1238	2862

These figures show an increase in mortality, but do not indicate the percentage mortality of the disease.

Adams¹ recently brought forward figures that had been collected from St. Thomas's Hospital, together with others already published by Love² from the London Hospital. They showed that the percentage rate of mortality in appendicitis is by no means as low as the general impression would indicate. In both these hospitals two methods are adopted in the treatment of the disease—one in which immediate operation is undertaken, and the other where delay is advocated if the patient is in the third to

sixth day of the disease. The patient is watched, and if the condition is progressive, operation is undertaken.

The percentage case mortality is weighted by the cases of general peritonitis; Adams remarks that, if we omit these cases, "the St. Thomas's mortality comes down to 2.7 per cent. and that of the London to 3.5. These are very respectable figures, and seem to me to justify the gospel of immediate surgical treatment."

Further improvement in these figures can only be obtained by the early recognition of the disease, and especially is this the case in children, in whom the interval between the disease, being limited to the appendix region and general peritonitis is frequently short. The advantage of delay in operation seems very doubtful; all its advocates appear to be agreed that it can only be followed under hospital conditions. This teaching must have its repercussion first on the general practitioner and later on the general public, and does not appear to me to be safe.

When an analysis of the cases treated on delayed lines is made it appears that at the London Hospital 109 cases out of a total of 341 were "unsuccessfully delayed," and at St. Thomas's Hospital 71 out of 214—in each case approximately one in three. It seems probable that the cases "unsuccessfully delayed" must be in a worse condition to withstand operative intervention than if they had been operated on when first diagnosed; the mortality in these cases is in fact higher than that of cases of local abscess which underwent immediate operation—at the London Hospital 6.4 per cent. compared with 4.6 per cent., and at St. Thomas's Hospital 14 per cent. compared with 4.2 per cent.

The figures at University College Hospital are taken for five years—from 1921 to 1925. The practice at this hospital has been to treat all cases diagnosed appendicitis by an emergency operation, irrespective of the day of the disease or the presence or absence of an abscess. Further, all cases diagnosed appendicitis are admitted to the surgical side, and are therefore under "one man control"—a point of considerable importance, as Adams has pointed out.

We therefore get in these figures the result on the case mortality of one quite definite line of treatment—namely, immediate operation. The cases have been divided into those that were drained and those cases in which the abdominal wall was sutured and no drainage employed. This gives a rough idea of the character of the disease, allowing for slight variations in the treatment of different operators; those cases that were drained either had general peritonitis or considerable collections of localized pus. The total number of cases was 602; of these, 274 were closed and 328 drained; 21 died (3.5 per cent.).

The number of cases of general peritonitis amongst these was 62, or about one-tenth, and the case mortality was 11—a percentage of 17.7. The mortality in the remaining 540 cases was 10 (1.8 per cent.). Two died of obstruction other than paralytic ileus, five with localized abscess, one of abscess of the lung, one from pneumonia, and one from spreading cellulitis of the abdominal wall. Among the cases dealt with, 95 were children under the age of 14; the mortality in these cases was 6—a percentage of 6.3 as compared with the above average of 3.5; of these 6 cases 5 died of general peritonitis. These figures bear out the seriousness of the disease in children, and the necessity of early diagnosis and immediate operation.

This fact is further brought out in the Registrar-General's figures for appendicitis and typhlitis for 1925, in which the deaths are arranged according to ages.

Years.	Males.	Females.	Total.
0-15	415	341	756
15-25	307	180	487
25-45	351	263	614
45-65	383	323	706
65-75	126	96	222
75 and over	42	35	77

It is stated by most authorities that the third to the sixth day is the dangerous stage at which to operate. It would appear probable that this statement rests on false premisses. Where immediate operation has not been advocated the cases are treated medically, and a number of