hospital. On scrutinizing the data as $(aB) = (B) - (AB)$ or $50 - 2 = 48$, and $(a) = (N) - (A)$ or $100 - 40 = 60$, we have $\frac{(aB)}{(a)} = \frac{48}{60} = 0.8$. So $\frac{(AB)}{(A)} \cdot \frac{(aB)}{(a)} = 0.05 : 0.8$.

The proportion, therefore, of the blind among the deaf is 5 per cent., while that of the blind among the not-deaf is 80 per cent. The ratio of the two is 0.0625 : 1. To determine the measure of association by the proposed method we must remember that we are measuring the association of blindness and deafness, so we must find the value of $0.0625 - 1$, which gives the negative decimal -0.9375 , showing that there is a strong negative association, or a disassociation, between blindness and deafness in this assemblage.

A contentious director, if he were totally ignorant of medical etiquette, might say that "As blindness in this hospital protects from deafness, and deafness from blindness, it is obvious that the ophthalmic surgeon is a very good aurist but very inefficient at eyework, and vice versa"; and he might then move that the aurist and the ophthalmic surgeon should exchange their offices.

All aspersions on these worthy men would be removed if it were pointed out that an analogous instance occurred in the adjoining general hospital, where there were 10 cases of fractures and 20 cases of tonsillitis, and no patient suffered from both these affections. The last speaker would perhaps wish that the eminent surgeon and the no less distinguished physician should exchange their parts, on the ground that the surgeon was excellent at curing throats (which he had never seen) but no good for broken bones.

The above will give the reader some idea of the pitfalls that lie in a hasty generalization from statistical tables, unless great care is taken to consider the assemblage from which the tables are drawn. It must always be remembered that hospitals are artificial assemblages: for example, the patients of lock hospitals all suffer (it may be in very different ways) from one cause; whilst those of general hospitals suffer from causes that have little if any association with each other.

To avoid the peculiarities of special assemblages one may naturally turn to the census returns of the United Kingdom, but unfortunately these are useless for most medical purposes, for example, to determine the value of a certain course of treatment, for they do not give all the data required.

I have before me a paper written by an antivaccinationist; the statistics given are analogous to my first example: "99 per cent. of those who had red hair were Canadians." In no instance are we told the number (N) of the assemblage under consideration, we are frequently told the number (V S) of those who had been vaccinated that got small-pox, but never the number (v S) of those that had not been vaccinated that suffered from small-pox, and never the number of the vaccinated (V) or that of the unvaccinated (v) in a district. In 1887 we are told that in the neighbourhood of Sheffield "on they went, vaccinating and revaccinating, and still the small-pox epidemic spread. There were no less than 7,000 cases of small-pox, and alas! 600 deaths, and still the small-pox went on."

This is mere rant. What proportion of the 7,000 cases had been vaccinated? But even if this were given we could draw no conclusion as to the value, or want of value, of vaccination, unless we were given (N), (V) and (V S), as well as the (S) which is given as 7,000. If it is desired to consider the association of vaccination, small-pox, and fatal cases of small-pox, 8 class-frequencies must be given before any conclusion as to the value of vaccination could be drawn with reference to small-pox and its fatalities.

Statistics can be wielded effectively only by those who have taken the trouble to learn how to use them. In order to draw a conclusion about the association of two attributes A and B, it is necessary to compare the proportion, or the percentage, of the B's among the A's with that of the B's among the not-A's, or $\frac{(AB)}{(A)} \cdot \frac{(aB)}{(a)}$.

It is useless to compare the percentage of the B's among the A's with that of the not-B's among the A's, as is not unfrequently done by company promoters and antivaccinationists. If $\frac{(AB)}{(A)}$ and $\frac{(Ab)}{(A)}$ are compared, it is clear that the canon about the independence of the four class-frequencies has not been obeyed, for $(A) = (AB) + (Ab)$;

so only two independent class-frequencies have been given.

Enough has been said to guard the reader from being misled by conclusions drawn from insufficient statistical data.

REMARKS ON THE PATHOGENESIS OF DEFICIENCY DISEASES AND ON PELLAGRA.

BY

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HAVING seen the interesting report by Colonel McCarrison (of the Pasteur Institute of Southern India) on the changes in the organs of pigeons fed on polished rice and suffering from polyneuritis, I wish to call the attention of those interested in this very important group of researches to some results which I obtained several years ago when working on other forms of deficiency diseases; they were published in the summer of 1915, in the Italian review *Sperimentale*, but remained completely unnoticed.

After working for some years subsequent to 1911 on the pathogenesis of pellagra, this problem (at that time less known than now) was carefully examined by me from several points of view. In consequence I was unable to uphold the photodynamic theory of Raubitschek, because I found that the exposure to light of white mice fed on maize neither shortened their life nor did them more harm than maize feeding in the dark.¹ I could not find any precipitins in the serum of pellagra patients (for maize extracts or maize protein) as some had asserted, nor could I demonstrate any positive complement fixation between serums of pellagra patients and maize extracts.²

Other researches were directed towards the study of general and local reactions of pellagra patients to the injection of maize extracts under the skin. There was some positive expression of hypersensitivity, owing, perhaps, to sensitization of those pellagra patients living on maize meal to maize proteins, through the intestinal tract. My countryman Volpino has worked much on the hypersensitivity reactions of pellagra patients to maize extracts.³

Without reviewing further my former experimental work, I may say that later on I adopted the conclusion, which was rapidly gaining favour, that notwithstanding new theories on the infectious nature of the disease (I am thinking chiefly of Sambon's Simulium theory), pellagra must be regarded as a deficiency disease, and that the problem of its etiology ought to be studied as far as possible according to the new methods developed chiefly by American investigators. We have not yet succeeded in finding an animal in which pellagra can develop so rapidly and typically as, for example, polyneuritis (beriberi) in fowls and pigeons. The new researches of Chittenden and Underhill⁴ seem to show that dogs can become ill with pellagrous symptoms when fed on a special diet, and a long series of investigators have studied the effects of maize feeding on rabbits, and especially on guinea-pigs. I, too, have studied the maidism of guinea-pigs from different points of view, and these are the experimental researches which I think it would be useful to resume in order to make a comparison with the interesting data of McCarrison.

It is well known that exclusive maize feeding very quickly brings about a severe pathological condition in guinea-pigs, which die in a few weeks after having lost about one-third of their weight. In the last period of their life the animals suffer from loss of hair, weakness of the legs, and diarrhoea. We know also from the work of Holst and Fröhlich,⁵ and others after them, that guinea-pigs, when fed on cereal grains alone (oats, wheat), develop a typical scurvy-like condition with lesions of bones, bone-marrow, teeth, and blood vessels—these last occasioning a real haemorrhagic diathesis. This scurvy-like condition of guinea-pigs (which is most quickly produced by oat feeding) was considered by Fröhlich, Holst, Funk,⁶ and most scientists to be the result of lack of accessory food factors or vitamins. The features of the experimental diseases were compared to those of the scurvy of men, and chiefly to Barlow's disease. Recently

McCollum and his co-workers have denied the existence of antiscorbutic vitamins, and have shown that there are only two accessory growth-promoting and life-maintaining factors, one water-soluble A and the other fat-soluble B. Now⁷ the scorbutic condition of guinea-pigs fed on oats would be due less to a lack of accessory factors in the diet—that is, to a chemical deficiency of it—than to a physical character of the cereal grains leading to undue retention and putrefaction of faeces in the enlarged caecum of the animals and thereby to intoxication, with changes in the walls of the vessels and perhaps secondary infections by special bacteria, like those described in the lesions of bones and in the blood by Jackson and Moody.⁸ Nevertheless, McCollum, N. Simmonds, and Pitz point to deficiency of factor A in all cereal grains and also in oat kernel.⁹ And although they do not recognize scurvy as an avitaminosis, we can still admit that qualitative deficiency of proteins, lack or deficiency of certain accessory factors (chiefly fat-soluble), and of salts play a rôle in the inadequacy of cereal grains when given alone to support the life of animals, with or without other chemical disturbances (acidosis),¹⁰ or with physical conditions of the food (McCollum).

Now I worked in 1913-14 on the effects of maize feeding on guinea-pigs, and published in the *Ricerche di biologia* (Società tipografica fiorentina, 1914) a short report followed by a long paper in the *Sperimentale* (1915, fasc. 4).¹¹ I at first tried to show the differences between the more typical scurvy (oat feeding) and the conditions produced by feeding on maize, which is the cereal more related to the etiology of pellagra; also between these two pathological conditions and simple starvation (by complete suppression of food). Like McCarrison I measured the weights of some organs and found the following relative numbers (weight of the organ in proportion to the body weight at death = 100), which of course are average results for many individuals in each group.

	Liver.	Spleen.	Suprarenal Glands.			
			Male.	Female.	Pregnant Female.	Average
Starving guinea-pigs...	3.20 %	0.10 %	—	—	—	0.18 %
Oat-fed guinea-pigs ...	3.76 %	0.10 %	0.22 %	0.27 %	0.33 %	0.27 %
Maize-fed guinea-pigs	3.90 %	0.14 %	0.20 %	0.24 %	—	0.22 %
Normal guinea-pigs ..	3.82 %	0.12 %	0.10 %	0.12 %	0.14 %	0.12 %

Thus in all these conditions the adrenal glands are enlarged, principally in oat-eating and maize-eating guinea-pigs. The loss of body weight is only one-third, while the relative weight of the adrenals is about doubled.

The spleen was reduced in weight, chiefly in the oat-eating and in the starving animals, and some evidence was found of an atrophic condition of this organ, as McCarrison has seen in his pigeons.

My histological observations can be summarized as follows:

The organs which are the most affected in guinea-pigs fed on maize are the spleen, the thyroid, and the suprarenal glands. The spleen shows sclerotic lesions with increase of elastic and fibrous tissue and reduction of lymphocytes in the folliculi. The thyroid shows, in the first days of maize diet, hyperaemia and often proliferation of alveolar epithelium, then haemorrhagic changes and later on sclerosis are prominent.

These changes, as far as I know, have not been observed before, but they may be compared with those remarked by some observers in the thyroid of starving animals or of animals fed on other special diets. The suprarenal glands show hyperaemia, enlargement of minute vessels, degenerative changes in the cortical cells with disappearance of the normal lipoids (Sudan III coloured substances), perhaps slight proliferation in the cells of the outer cortical layer; the reticular fibres (*Gitterfasern*) become thicker, the reaction with chromium salts in the medullaris seems to be less marked. Degenerative changes were prominent in the central nervous system. By means of Nissl's method I observed signs of decay in the anterior horn cells of the spinal cord and in Purkinje cells of the cerebellum, and by Marchi's method frequent irregular fresh degeneration of all sorts of medullated fibres. The changes in the bone marrow were of the same kind, but in

a less degree than those observed by Fröhlich and Holst as the result of other cereal feeding. Less marked were the lesions of the liver (some degeneration of liver cells, some hyperaemia, some hypertrophy of Kupffer cells, sometimes perhaps proliferation of these cells), of the intestinal tract, of the kidney, and of the heart.

Guinea-pigs fed on oats had much more marked haemorrhagic lesions; the haemorrhagic diathesis seems to me to belong to the typical scorbutic condition of these animals. As already pointed out by Centanni and Galassi,¹² maize feeding brings about an attenuated scorbutic condition, but the results of my experiments show that the central nervous symptoms, fall of hair, sclerosis of spleen and thyroid, are more marked than in scurvy. As regards the effects of starvation, which were already well known, I confirm the difference from the above named unilateral diets: we have no true sclerosis of organs, lipoids disappear in a much more marked degree from the cortex of the adrenal glands, we have quite different conditions in the bone marrow (the so-called *Hungermark* of the Germans). Histologically, death from maize eating is not death from starvation, but involves deep metabolic changes, as in other real deficiency diseases and in some intoxications.

In order to study the reason of the severe injury caused to the organism by maize feeding I tried to supplement the maize meal or maize kernel with many substances. At that time the important work of McCollum was still unknown, or at least I was not acquainted with results of his which appeared later. Thus I thought first to add some protein or peptone to the maize meal in order to see whether the failure of this grain to maintain metabolism was due to deficiency of protein. The addition to the maize meal of casein (pure casein Merk), or peptone, or amino-acids, such as tyrosin and tryptophan, tried in different series of guinea-pigs, produced no definite improvement of the diet. One year later (1916) McCollum, Simmonds, and Pitz,¹³ who worked with their usual method on growing white rats, showed that the maize protein contained all the necessary amino-acids, but not all in the most favourable proportions, that at any rate the deficiency of maize could not be sufficiently made good with casein, and that the protein factor had not the paramount importance for rats that it seemed to have for other animals. Hogan,¹⁴ too, has seen that for rats the first limiting factor in the maize diet is the lack of salts, but that the deficiency of the proteins of maize is, on the whole, less important. I did not take into consideration the salts, but I had already written that the protein deficiency of maize does not seem to have any great importance for guinea-pigs in the development of maldism,¹⁵ and Hogan's experiment of supplementing maize with casein had been made by me on guinea-pigs with the same negative results. Hogan says that for pigs things are on a different basis; protein is here the first limiting factor, as Passerini had already demonstrated in very accurate experiments, which were, of course, unknown to the Americans.¹⁶ I tried further to supplement maize with green food, as Holst and Fröhlich had shown that green vegetables prevent the development of scurvy. I repeated these experiments on guinea-pigs suffering from the pathological condition which arises from exclusive maize feeding, and seems to me (see above) to differ from typical scurvy (from oat and wheat feeding). I found that a quantity as small as 10 grams a day of fresh cabbage produced in every animal a remarkable corrective action. Animals eating maize meal alone (and water) die after an average period of eighteen days (there are great individual differences, some animals living only a few days, others weeks); animals eating maize meal *plus* 10 grams of cabbage died after twenty-five days, and showed loss of weight only in the last days. A few months after the publication of my results in the *Sperimentale* (1915, July-August), I read¹⁷ that Sandwith had confirmed this supplementing value of fresh cabbage for maize eating guinea-pigs. He stated that even smaller quantities of green food were active in this direction. As I had seen that the protein factor was not of much value, and besides this, that the protein content of the active quantities of cabbage was very low, I thought that perhaps there might be in cabbage some accessory factor of unknown composition, some lipid-bound substance (I had in mind the results of Stepp¹⁸), or some vitamine-like principle; accordingly I tried to test the action of alcoholic extracts of cabbage

with positive results of a prolongation of the average life of maize-meal-eating guinea-pigs. In the light of the new ideas of McCollum I venture to say that with my alcoholic extracts (made with acidulated alcohol at 37°) I partly supplemented the fat-soluble factor A, which is certainly lacking in all cereal grains and in maize meal too, and is abundant in all leaves. Lately, Osborne and Mendel¹⁹ have found in cabbage a lack of water-soluble vitamin B, and therefore in alcoholic extract we may assume that factor A is present.

I tried also to supplement maize meal with alcoholic extract of maize bran, but to no purpose; this again shows that the active substance of alcoholic extracts of cabbage leaves is something which is present neither in maize meal nor in maize bran—that is, something lacking in the whole cereal grain, in the endosperm as well as in the aleuronic layer and embryo; this is the case with factor A, while factor B must be present in good bran with much of the outer layers and embryos of the seed.

I can also state that alcoholic extracts of liver (fresh liver of healthy guinea-pigs) prolonged the life of maize-meal-eating guinea-pigs a little; the active substance was present in animal organs too. This may perhaps be compared with the experiments of Osborne and Mendel, who found the liver, heart, and kidney (of pigs) very rich in growth-promoting vitamin for rats,²⁰ and of Eddy, who isolated a growth-promoting substance from sheep's pancreas. Thus I came to the conclusion that in animal organs and in the green parts of plants there must be some alcohol-soluble body which diminishes the harmful action of maize diet on guinea-pigs; but with the means at my disposal I could go no further in my analysis.

It is well to remember, too, that I found a diminution of adrenalin in the suprarenal glands of maize-eating animals, using the biological method of Fraenkel (action of suprarenal glands ground up and suspended in saline solution on the uterus of virgin rabbits, and registration of the contraction of the muscular organ); contrary to the results of experiments by McCarrison on pigeons fed on polished rice, pointing to an increase of adrenalin. The difference may be attributed to the different conditions of experimental work and of diet and to the zoological remoteness of the animals used. My work on the etiology of pellagra did not produce conclusive results, but it has established certain facts which may be important in the etiology and pathogenesis of maidism in guinea-pigs and of pellagra in man. I do not assume the identity of these two conditions; the differences are obvious, but there are some resemblances too. It is a fact that maidism is an experimental deficiency disease due to the lack in maize of the elements necessary to maintain animals. McCollum, Simmonds, and Parsons²¹ do not look upon pellagra as a real avitaminosis in the sense used by Funk and do not recognize a pellagra vitamin, but still they maintain that the experimental symptom-complex obtained by Chittenden and Underhill in dogs is to be attributed to protein factors, partly to lack of factor A and of salts. For the maidism of guinea-pigs we may still admit a complicated deficiency of maize meal, and we may state that green vegetables and fresh animal organs contain corrective substances. Maidism, at any rate, has features which I think separate it from simple starvation and from typical scurvy.

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AT the commencement exercises of the New York University and Bellevue Hospital Medical College it was announced that the institution would in future admit women and would grant them the degree of M.D. on the same terms as men.

A Collective Investigation OF TEN THOUSAND RECRUITS WITH DOUBTFUL HEART CONDITIONS.

Conducted at the National Hospital for Diseases of the Heart by C. CHAPMAN GIBBS, R. O. MOON, S. RUSSELL WELLS, P. HAMILL, FREDERICK W. PRICE, and J. STRICKLAND GOODALL.

REPORT III.*

COMPILED BY

S. RUSSELL WELLS, M.D., B.Sc.

THE ETIOLOGY OF AORTIC REGURGITATION.

Syphilis.

Of the 307 cases 11 gave a history of syphilis, but in no less than 7 of these there was a definite history of rheumatic fever, and of the remaining 4, the first, a carman aged 39, had had a fever of a doubtful nature which may have been acute rheumatism, and presented definite signs of mitral stenosis and regurgitation as well as of aortic regurgitation; his syphilis had been acquired 36 years before examination. The second was a man of 30 years of age, who said he had had rheumatism, which he described as "muscular," but which laid him up for three months when he was 28; as, however, he stated he had had gonorrhoea no less than eight times, the true rheumatic nature of the affection must at least be regarded as doubtful, probably it was gonorrhoeal rheumatism. The third, aged 34, gave no history of illness beyond his syphilis five years ago, except scarlet fever; he showed signs of mitral regurgitation which was probably secondary, as he had albumin in his urine and other signs of failing circulation. The fourth, a man of 30, gave no history of any illness other than syphilis four years ago except tonsillitis eight years before, and influenza. He was classified as pure aortic regurgitation. Thus, out of the 11 cases, in 4 at the most, that is, 36.4 per cent., and possibly in only 3 (27.3 per cent.), can syphilis alone be credited with being the cause of the aortic regurgitation.

TABLE XIII.—Comparing all the Cases of Aortic Regurgitation dealt with, with those giving a Syphilitic History.

	No. of Cases.	With Rh. Fever.	With Rh. G.P., or Ch	Without Rh. History
Total Ao. R. ...	307	162=52.8%	73=23.8%	72=23.4%
Ao. R. and syphilis ...	11	7=63.6%	1=9.1%	3=27.3%

Making due allowance for the small numbers involved in the case of syphilis, the percentages are very similar. This suggests that the coincidence of syphilis and aortic regurgitation in the three or four cases where there was no definite history of rheumatic fever may be fortuitous. It may be objected that we are dependent in these cases upon the man's word alone for a history of syphilis, and that frequently its presence has been concealed. No doubt it would have been better, had it been possible, to have determined the Wassermann reaction in every case. This, of course, was impracticable, but, as has been pointed out in a previous report, by reason of the exceptional circumstances of these examinations there was far less likelihood of concealment than usual. Moreover, the results quite confirm the impressions gained on taking the Wassermann reaction of a series of hospital out-patients suffering from aortic regurgitation.

Ratio of Pure to Mixed Lesions.—We may record, for what it is worth, the fact that the proportion of pure aortic to mixed lesions is higher in the syphilitic cases than in the total aortic regurgitants with a history of rheumatic fever—that is, 1.2 as against 0.76. Of the syphilitic cases without a definite history of rheumatic fever 2 were pure aortic and 2 mixed lesions. Very little importance can be attached to these figures, as the number of syphilitic cases is too small.

It will be seen that the investigation of these cases leads to the conclusion that syphilis is not of much importance as a cause of aortic regurgitation in the case of men

* Concluded from p. 514.